09720952 Page 1

07/15/2002

STN Research

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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Dec 17	The CA Lexicon available in the CAPLUS and CA files
NEWS 3	Feb 06	Engineering Information Encompass files have new names
NEWS 4	Feb 16	TOXLINE no longer being updated
NEWS 5	Apr 23	Search Derwent WPINDEX by chemical structure
NEWS 6	Apr 23	PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
NEWS 7	May 07	DGENE Reload
NEWS 8	Jun 20	Published patent applications (A1) are now in USPATFULL
NEWS 9	JUL 13	New SDI alert frequency now available in Derwent's DWPI and DPCI
NEWS 10	Aug 23	In-process records and more frequent updates now in MEDLINE
NEWS 11	Aug 23	PAGE IMAGES FOR 1947-1966 RECORDS IN CAPLUS AND CA
NEWS 12	Aug 23	Adis Newsletters (ADISNEWS) now available on STN
NEWS 13	Sep 17	IMSworld Pharmaceutical Company Directory name change to PHARMASEARCH
NEWS 14	Oct 09	Korean abstracts now included in Derwent World Patents Index
NEWS 15	Oct 09	Number of Derwent World Patents Index updates increased
NEWS 16	Oct 15	Calculated properties now in the REGISTRY/ZREGISTRY File
NEWS 17	Oct 22	Over 1 million reactions added to CASREACT
NEWS 18	Oct 22	DGENE GETSIM has been improved
NEWS 19	Oct 29	AAASD no longer available
NEWS 20	Nov 19	New Search Capabilities USPATFULL and USPAT2
NEWS 21	Nov 19	TOXCENTER(SM) - new toxicology file now available on STN

NEWS EXPRESS	August 15 CURRENT WINDOWS VERSION IS V6.0c, CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP), AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

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Golam Shameem

FILE 'HOME' ENTERED AT 18:07:13 ON 27 NOV 2001

=> file registry

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.15	0.15

FILE 'REGISTRY' ENTERED AT 18:07:25 ON 27 NOV 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

STRUCTURE FILE UPDATES: 26 NOV 2001 HIGHEST RN 371913-98-3
DICTIONARY FILE UPDATES: 26 NOV 2001 HIGHEST RN 371913-98-3

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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L1 STRUCTURE UPLOADED

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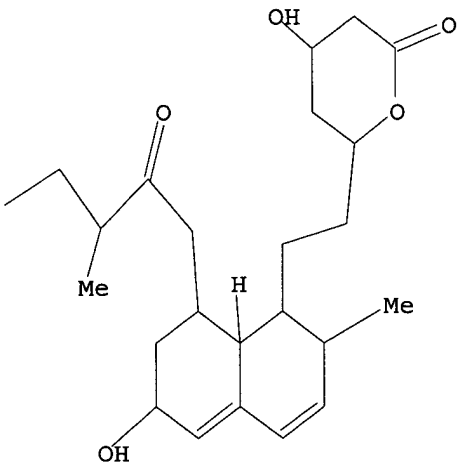

Structure attributes must be viewed using STN Express query preparation.

Golam Shameem

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SAMPLE SCREEN SEARCH COMPLETED -     25 TO ITERATE

100.0% PROCESSED      25 ITERATIONS                                  0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          200 TO      800
PROJECTED ANSWERS:               0 TO        0

L2             0 SEA SSS SAM L1

=> s l1 sss full
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FULL SCREEN SEARCH COMPLETED -    499 TO ITERATE

100.0% PROCESSED     499 ITERATIONS                                  0 ANSWERS
SEARCH TIME: 00.00.01

L3             0 SEA SSS FUL L1

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L4 HAS NO ANSWERS
L4                STR
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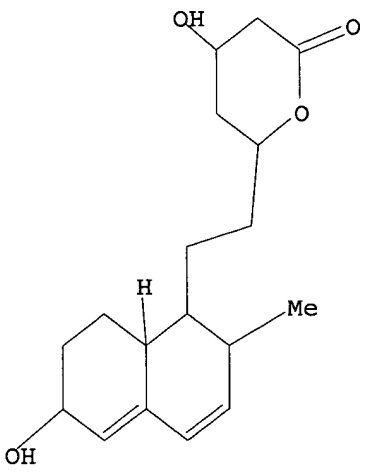

Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED -    344 TO ITERATE

100.0% PROCESSED     344 ITERATIONS                                  8 ANSWERS
```

Golam Shameem

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 5768 TO 7992
PROJECTED ANSWERS: 8 TO 329

L5 8 SEA SSS SAM L4

=> s l4 sss full
FULL SEARCH INITIATED 18:10:40 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 7156 TO ITERATE

100.0% PROCESSED 7156 ITERATIONS 148 ANSWERS
SEARCH TIME: 00.00.01

L6 148 SEA SSS FUL L4

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	268.36	268.51

FILE 'CAPLUS' ENTERED AT 18:10:51 ON 27 NOV 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1947 - 27 Nov 2001 VOL 135 ISS 23
FILE LAST UPDATED: 26 Nov 2001 (20011126/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

CAplus now provides online access to patents and literature covered in CA from 1947 to the present. On April 22, 2001, bibliographic information and abstracts were added for over 2.2 million references published in CA from 1947 to 1966.

The CA Lexicon is now available in the Controlled Term (/CT) field. Enter HELP LEXICON for full details.

=> d his

(FILE 'HOME' ENTERED AT 18:07:13 ON 27 NOV 2001)

FILE 'REGISTRY' ENTERED AT 18:07:25 ON 27 NOV 2001
L1 STRUCTURE UPLOADED
L2 0 S L1
L3 0 S L1 SSS FULL
L4 STRUCTURE UPLOADED
L5 8 S L4
L6 148 S L4 SSS FULL

FILE 'CAPLUS' ENTERED AT 18:10:51 ON 27 NOV 2001

=> s l6
L7 69 L6

=> s l6/proc
69 L6
3056865 PROC/RL
L8 7 L6/PROC
(L6 (L) PROC/RL)

=> d l7 ibib abs hitstr tot

L7 ANSWER 1 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:753814 CAPLUS
DOCUMENT NUMBER: 135:287598
TITLE: Pravastatin manufacture with Microtetraspora
INVENTOR(S): Okabe, Mitsuyasu
PATENT ASSIGNEE(S): Mercian Corp., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

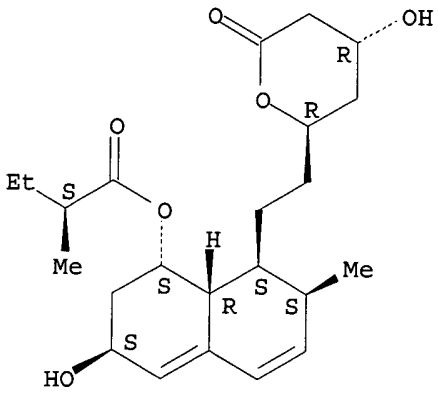
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001286293	A2	20011016	JP 2000-104278	20000406

AB Pravastatin (I), an hypolipemic, is manufd. with Microtetraspora such as M. recticatena from mevastatin or its open ring form. The I may be a lactone form or a salt. The physiol. and morphol. characteristics of the microorganism were also given.

IT **85956-22-5P**, Pravastatin lactone
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pravastatin manuf. with Microtetraspora)

RN 85956-22-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 2 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:472486 CAPLUS
DOCUMENT NUMBER: 135:56086
TITLE: Cyclooxygenase 2 inhibitor-~~HMG-CoA reductase inhibitor~~ combination for treating neurodegenerative diseases, especially Alzheimer's disease
INVENTOR(S): Waldstreicher, Joanne
PATENT ASSIGNEE(S): Merck & Co. Inc., USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001045698	A1	20010628	WO 2000-US34069	20001218

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

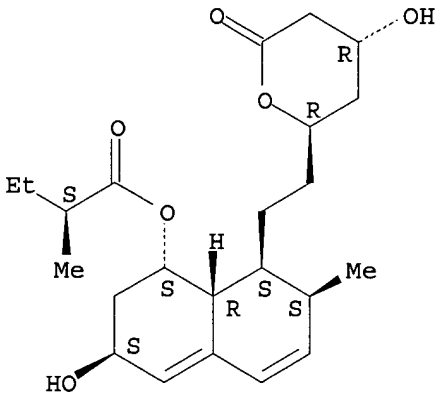
PRIORITY APPLN. INFO.: US 1999-172926 P 19991221

AB The invention provides a drug combination comprised of an HMG-CoA reductase inhibitor and a selective COX-2 inhibitor, which is useful for treating, preventing, delaying the onset of and/or reducing the risk of developing Alzheimer's disease. One object of the invention is to administer the above-described combination therapy to people who do not yet show clin. signs of Alzheimer's disease, but who are at risk of developing Alzheimer's disease. These individuals may already show signs of mild cognitive impairment. Toward this end, the invention provides methods for preventing or reducing the risk of developing Alzheimer's by administering the above-described combination therapy to the at risk persons. Such treatment may halt or reduce the rate of further cognitive decline or, in fact, reverse cognitive decline. The invention also provides a method for preventing cognitive impairment or dementia, reducing the risk of cognitive decline or impairment or reducing cognitive

decline or impairment resulting from stroke, stroke, cerebral ischemia or demyelinating disorders.

IT **85956-22-5**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase 2 inhibitor-HMG-CoA reductase inhibitor combination for treating neurodegenerative diseases, esp. Alzheimer's disease)
RN 85956-22-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2
REFERENCE(S): (1) Ducharme; US 5840746 A 1998 CAPLUS
(2) Scolnick, E; WO 9506470 1995 CAPLUS

L7 ANSWER 3 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:416764 CAPLUS
DOCUMENT NUMBER: 135:18608
TITLE: Process for recovering statin compounds from a fermentation broth
INVENTOR(S): Keri, Vilmos; Deak, Lajos; Forgacs, Ilona; Szabo, Csaba; Nagyne, Edit Arvai
PATENT ASSIGNEE(S): Biogal Gyogyszergyar Rt, Hung.; Teva Pharmaceuticals Usa, Inc.
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001039768	A1	20010607	WO 2000-US32391	20001128

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,

DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-168056 P 19991130

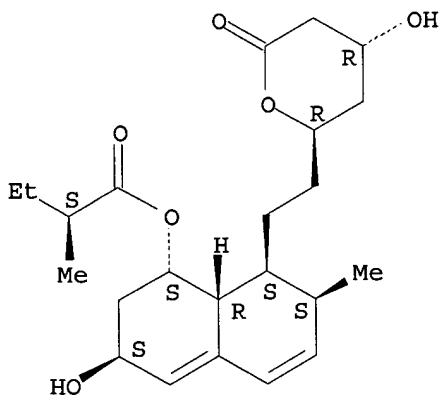
AB A novel process for recovering a compd. from a fermn. broth that includes the stages of forming an enriched soln. of the compd. by extn., obtaining a salt of the compd. from the enriched soln., purifying a salt of the compd. and exchanging the salt of the compd. to a metal salt of the compd. is disclosed. Thus, pravastatin was extd. by iso-Bu acetate from fermn. broth which had been acidified to pH 2.5 by sulfuric acid. The the pH of the solvent ext. was then adjusted to 11 by the addn. of aq. ammonium hydroxide and the resulting aq. pravastatin soln. was re-acidified and then back extd. with iso-Bu acetate. After the iso-Bu acetate ext. had been partially dried and decolorized with activated charcoal, ammonia gas was added to the headspace of the soln. until all pptn. ceased. The pptd. ammonium pravastatin salt was collected by filtration, washed with solvents, dild. in water, acetone and iso-Bu acetate, crystd. by the addn. of solid ammonium chloride. The crystd. ammonium pravastatin further crystd. in isobutanol. The ammonium pravastatin salt crystals were then dissolved in a water and iso-Bu acetate was added. The soln. was acidified to ph 2-4 with sulfuric acid, washed with water and the pravastatin was converted to its sodium slat by the intermittent addn. of sodium hydroxide. Excess sodium ions were removed by ion exchange and the sodium pravastatin salt was crystd. in a water/acetonitrile/acetone solvent. A sodium pravastatin yield of 65% with a purity of 99.3% was obtained with this process.

IT **85956-22-5P**, Pravastatin lactone
RL: BYP (Byproduct); PREP (Preparation)
(process for recovering statin compds. from a fermn. broth)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4

REFERENCE(S):
(1) Furuya; US 5153124 A 1992 CAPLUS
(2) Gist-Brocades; WO 9837220 A 1998 CAPLUS
(3) Gist-Brocades; WO 991049 A 1999
(4) Teva Pharmaceuticals Usa Inc; WO 0046175 A1 2000 CAPLUS

L7 ANSWER 4 OF 69 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:334067 CAPLUS

Golam Shameem

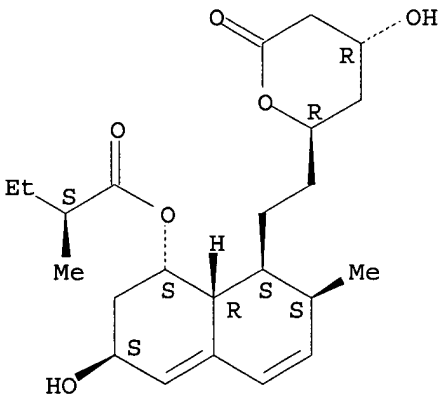
DOCUMENT NUMBER: 135:225890
TITLE: Chromatographic purification of some 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors
AUTHOR(S): Grahek, R.; Milivojevic, D.; Bastarda, A.; Kracun, M.
CORPORATE SOURCE: Lek d.d., Research and Development, Ljubljana, 1526, Slovenia
SOURCE: J. Chromatogr., A (2001), 918(2), 319-324
CODEN: JCRAEY; ISSN: 0021-9673
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purifn. of pravastatin, simvastatin and lovastatin in the sodium salt or lactone form and of mevastatin in the lactone form by reversed-phase displacement chromatog. is presented. The mobile phases consisted of water or mixts. of water-methanol and water-acetonitrile. Six different displacers were successfully used. Up to 0.14 g of raw sample per g of stationary phase was loaded on a column packed with silica-based octadecyl phase. Crude substances from 85 to 88% chromatog. purity were purified and at least 99.5% purity was achieved.

IT **85956-22-5P**, Pravastatin lactone
RL: PUR (Purification or recovery); PREP (Preparation)
(chromatog. purifn. of 3-hydroxy-3-methylglutaryl CoA reductase inhibitors)

RN 85956-22-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 28
REFERENCE(S):
(1) Cardinali, F; J Chromatogr 1990, V499, P37 CAPLUS
(3) Deshmukh, R; J Chromatogr A 1998, V806, P77 CAPLUS
(4) Felinger, A; Biotechnol Bioeng 1993, V41, P134 CAPLUS
(5) Frenz, J; AIChE J 1985, V31, P400 CAPLUS
(6) Fujioka, T; Biochim Biophys Acta 1995, V1254, P7 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:247177 CAPLUS
DOCUMENT NUMBER: 134:275767

Golam Shameem

TITLE: Synergistic anti-hypercholesterolemic drug combination using an HMG-CoA reductase inhibitor with an ACAT inhibitor
INVENTOR(S): Chao, Yu-Sheng
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001022962	A1	20010405	WO 2000-US26414	20000926

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

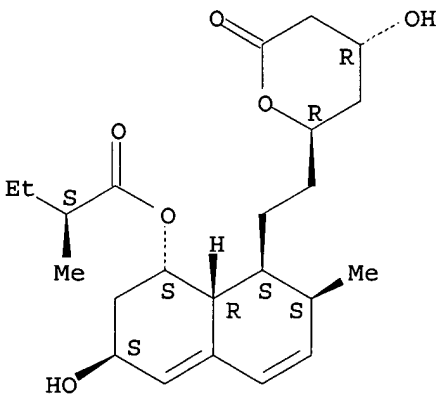
PRIORITY APPLN. INFO.: US 1999-157184 P 19990930

AB The invention provides a drug combination comprised of an HMG-CoA reductase inhibitor with an ACAT inhibitor in synergistic therapeutically effective amts., which is useful for reducing cholesterol synthesis, lowering plasma LDL cholesterol levels and lowering plasma triglyceride levels. Profound synergy can be achieved only when the ACAT inhibitor is administered in low dosage amts., above which the beneficial synergistic effects diminish and disappear.

IT **85956-22-5**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HMG-CoA reductase inhibitor-ACAT inhibitor synergistic hypocholesterolemic drug combination)

RN 85956-22-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



Golam Shameem

REFERENCE COUNT: 1
REFERENCE(S): (1) Warner-Lambert Company; WO 9716184 A1 1997 CAPLUS

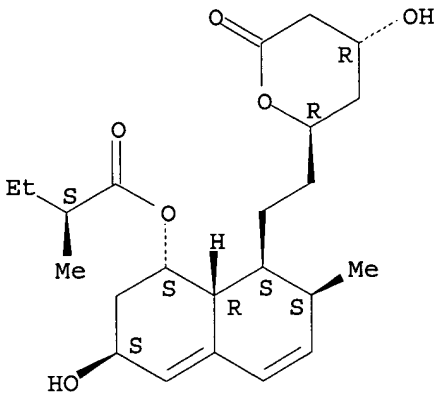
L7 ANSWER 6 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:146168 CAPLUS
DOCUMENT NUMBER: 134:320523
TITLE: A comparison of the effects of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors on the CYP3A4-dependent oxidation of mexazolam in vitro
AUTHOR(S): Ishigami, Michi; Honda, Tomoyo; Takasaki, Wataru; Ikeda, Toshihiko; Komai, Toru; Ito, Kiyomi; Sugiyama, Yuichi
CORPORATE SOURCE: Drug Metabolism and Pharmacokinetics Research Laboratories and Product Strategy Department, Sankyo Co., Ltd., Tokyo, Japan
SOURCE: Drug Metab. Dispos. (2001), 29(3), 282-288
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB HMG-CoA reductase inhibitors can be divided into two groups: those administered as the prodrug, i.e., the lactone form (e.g., simvastatin and lovastatin), and those administered in the active form, i.e., the acid form (e.g., pravastatin, fluvastatin, atorvastatin, and cerivastatin). In this study, the influence of the lactone and acid forms of various HMG-CoA reductase inhibitors on metab. by CYP3A4, a major cytochrome P 450 isoform in human liver, was investigated by detg. the in vitro inhibition const. (Ki value) using an antianxiety agent, mexazolam, as a probe substrate. In human liver microsomes, all the lactone forms tested inhibited the oxidative metab. of mexazolam more strongly than did the acid forms, which have lower partition coeff. (logD7.0) values. In addn., the degree of inhibition of mexazolam metab. tended to increase with an increasing logD7.0 value of the HMG-CoA reductase inhibitors among the lactone and acid forms. In particular, pravastatin (acid form), which has the lowest logD7.0 value, failed to inhibit CYP3A4 activity. Taking account of the lipophilicity of the inhibitors, in conjunction with the CYP3A4-inhibitory activity, could be very useful in predicting drug interactions between substrates of CYP3A4 and HMG-CoA reductase inhibitors.

IT **85956-22-5**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(comparative effects of HMG-CoA reductase inhibitors on CYP3A4-dependent oxidn. of mexazolam)

RN 85956-22-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 17
REFERENCE(S):
(1) Boberg, M; Drug Metab Dispos 1997, V25, P321 CAPLUS
(2) Boyd, R; J Clin Pharmacol 2000, V40, P91 CAPLUS
(4) Ito, K; Pharmacol Rev 1998, V50, P387 CAPLUS
(5) Kantola, T; Clin Pharmacol Ther 1998, V64, P58 CAPLUS
(6) Neuvonen, P; Clin Pharmacol Ther 1996, V60, P54 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:50841 CAPLUS
DOCUMENT NUMBER: 134:114919
TITLE: Microbial process for preparing pravastatin
INVENTOR(S): Jekkel, Antonia; Ambrus, Gabor; Ilkoy, Eva; Horvath, Ildiko; Konya, Attila; Szabo, Istvan Mihaly; Nagy, Zsuzsanna; Horvath, Gyula; Mozes, Julia; Barta, Istvan; Somogyi, Gyorgy; Salat, Janos; Boros, Sandor
PATENT ASSIGNEE(S): Gyogyszerkutato Intezet Kft., Hung.
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001004340	A1	20010118	WO 2000-HU66	20000629
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: HU 1999-2352 A 19990712
OTHER SOURCE(S): CASREACT 134:114919
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

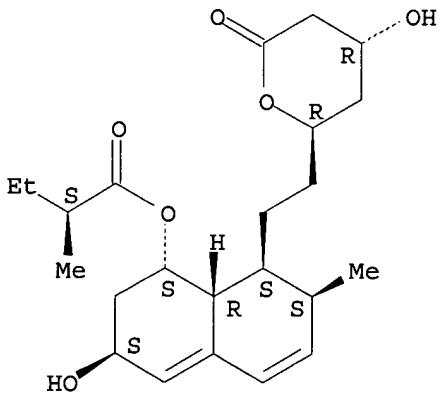
AB A process is provided for the bioconversion of compactin to pravastatin by a Micormonospora culture and the subsequent sepn. and purifn. of pravastatin. Specifically, the invention provides for the prepn. of a pravastatin salt of formula I from a compactin salt of formula II where R+ represents an alkali metal or ammonium ion. In this process, microorganisms of the genera Micromonospora are aerobically cultivated in a suitable fermn. medium at 25-32 .degree.C for a predetd. time at which a compactin salt is added and subsequently 6.beta.-hydroxylated to form the corresponding pravastatin salt. The pravastatin salt formed during the fermn. may then be sepd. from the fermn. broth by adsorption on an anionic ion exchange resin, or by extn. with a water immiscible org. solvent followed by the the prepn. of its lactone deriv. or its secondary amine salt as an intermediate, or by purifn. of an aq. alk. ext. obtained obtained from the org. solvent ext. by liq. chromatog. on a non-ionic adsorbing resin. Thus, Micromonospora strain IDR-P3 was cultured for 72 h at 32 .degree.C at which time 0.5 g/L sodium compactin was added to the fermn. broth which incubated for 72 h and which was followed by a second addn. of 0.5 g/L of the compactin sodium salt followed by an addnl. 72 h incubation. After this second incubation, 75% of the compactin had been converted to the sodium salt of pravastatin. The fermn. broth was centrifuged, the supernatant was saved and the cell pellet was water washed. The supernatant and the wash were combined, the pH was adjusted to 3.5-4.0 with sulfuric acid and the pravastatin was extd. with Et acetate. Then 150 mol% of dibenzyl amine was added to the ext. which was then concd. and held overnight at 0-5 .degree.C. The pptd. pravastatin dibenzyl ammonium salt was recovered by filtration, and was ultimately purified ion exchange chromatog.

IT **85956-22-5P**, Pravastatin lactone
RL: PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(microbial process for prepg. pravastatin)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2

Golam Shameem

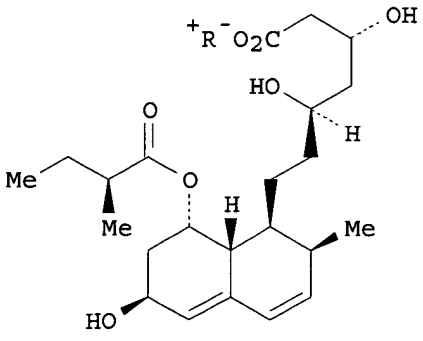
REFERENCE(S): (1) Massachusetts Inst Technology; WO 9640863 A 1996 CAPLUS
(2) Matsuoka, T; US 5179013 A 1993 CAPLUS

L7 ANSWER 8 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:50439 CAPLUS
DOCUMENT NUMBER: 134:114918
TITLE: Microbial process for preparing pravastatin
INVENTOR(S): Jekkel, Antonia; Ambrus, Gabor; Ilkoy, Eva; Horvath, Ildiko; Konya, Attila; Szabo, Istvan Mihaly; Nagy, Zsuzsanna; Horvath, Gyula; Mozes, Julianna; Barta, Istvan; Somogyi, Gyorgy; Salat, Janos; Boros, Sandor
PATENT ASSIGNEE(S): Ivax Corporation, USA
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001003647	A2	20010118	WO 2000-US19384	20000711
WO 2001003647	A3	20010628		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2000063492	A5	20010130	AU 2000-63492	20000711

PRIORITY APPLN. INFO.: HU 1999-2352 A 19990712
WO 2000-US19384 W 20000711

OTHER SOURCE(S): CASREACT 134:114918
GI



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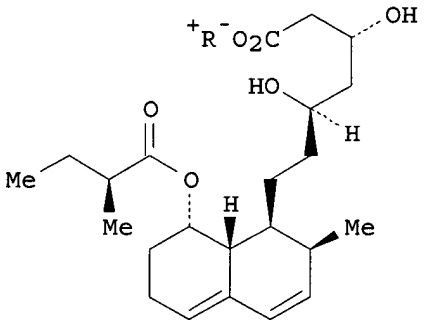


II

AB A process is provided for the bioconversion of compactin to pravastatin by a Micormonospora culture and the subsequent sepn. and purifn. of pravastatin. Specifically, the invention provides for the prepn. of a

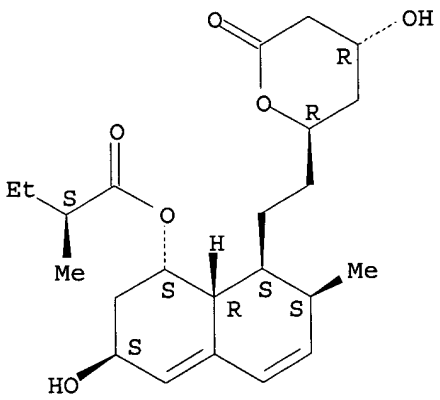
pravastatin salt of formula I from a compactin salt of formula II where R+ represents an alkali metal or ammonium ion. In this process, microorganisms of the genera Micromonospora are aerobically cultivated in a suitable fermn. medium at 25-32 .degree.C for a predetd. time at which a compactin salt is added and subsequently 6.beta.-hydroxylated to form the corresponding pravastatin salt. The pravastatin salt formed during the fermn. may then be sepd. from the fermn. broth by adsorption on an anionic ion exchange resin, or by extn. with a water immiscible org. solvent followed by the the prepn. of its lactone deriv. or its secondary amine salt as an intermediate, or by purifn. of an aq. alk. ext. obtained obtained from the org. solvent ext. by liq. chromatog. on a non-ionic adsorbing resin. Thus, Micromonospora strain IDR-P3 was cultured for 72 h at 32 .degree.C at which time 0.5 g/L sodium compactin was added to the fermn. broth which incubated for 72 h and which was followed by a second addn. of 0.5 g/L of the compactin sodium salt followed by an addnl. 72 h incubation. After this second incubation, 75% of the compactin had been converted to the sodium salt of pravastatin. The fermn. broth was centrifuged, the supernatant was saved and the cell pellet was water washed. The supernatant and the wash were combined, the pH was adjusted to 3.5-4.0 with sulfuric acid and the pravastatin was extd. with Et acetate. Then 150 mol% of dibenzyl amine was added to the ext. which was then concd. and held overnight at 0-5 .degree.C. The pptd. pravastatin dibenzyl ammonium salt was recovered by filtration, and was ultimately purified ion exchange chromatog.

IT **85956-22-5P**, Pravastatin lactone
RL: PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(microbial process for prepg. pravastatin)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 9 OF 69 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:2410 CAPLUS

DOCUMENT NUMBER: 134:193253

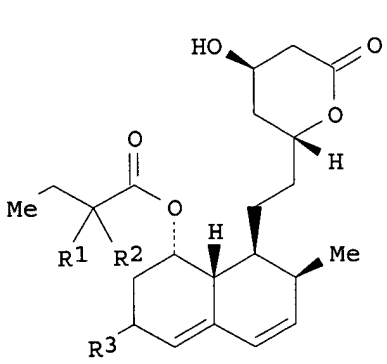
TITLE: Oxidation of HMG-CoA reductase inhibitors by tert-butoxyl and 1,1-diphenyl-2-picrylhydrazyl radicals: model reactions for predicting oxidatively sensitive compounds during preformulation

AUTHOR(S): Karki, Shyam B.; Treemaneekarn, Varaporn; Kaufman, Golam Shameem

Michael J.
CORPORATE SOURCE: Pharmaceutical Research and Development Department, Merck Research Laboratories, West Point, PA, 19486, USA

SOURCE: J. Pharm. Sci. (2000), 89(12), 1518-1524
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

GI



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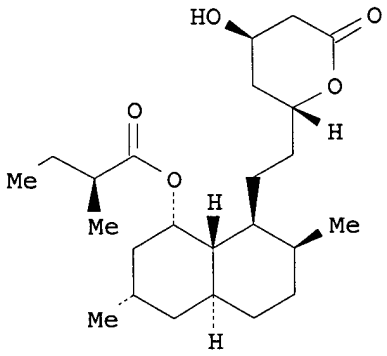


II

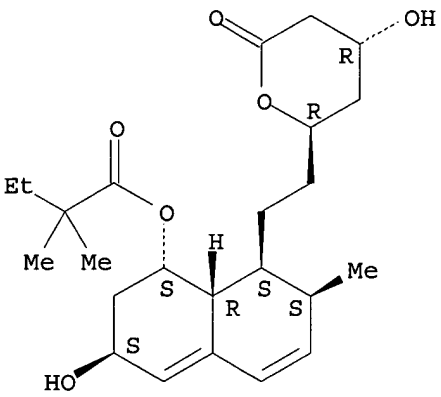
AB Hydrogen atom abstraction rate consts. for the reaction of tert-butoxyl and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical with the HMG-CoA reductase inhibitors lovastatin (I, R1 = H, R2 = .beta.-Me, R3 = .alpha.-Me), simvastatin (I, R1 = Me, R2 = Me, R3 = .alpha.-Me), and statins I (I, R1 = H, R2 = .beta.-Me, R3 = H), II (I, R1 = H, R2 = .beta.-Me, R3 = .beta.-CH2OH), III (II), and IV (I, R1 = Me, R2 = Me, R3 = .beta.-OH) were measured. This series of diene-contg. drugs is known to be prone to oxidn. The tert-butoxyl radical was generated by the thermolysis of di-tert-butylperoxyoxalate at 40.degree.C. A competitive kinetic method was used to det. the relative rate of hydrogen atom abstraction by tert-butoxyl radical to .beta.-scission. The abs. rate consts. were calcd. using the exptl. detd. product ratios of t-butanol to acetone and the known rate of .beta.-scission of tert-butoxyl radical. The rate consts. for the reaction with DPPH radical were measured spectrophotometrically by monitoring the loss of DPPH radical as a function of substrate concn. The rate consts. correlate well with the structure of the mols. studied. These kinetic techniques allow for oxidatively sensitive compds. to be identified early in the drug development cycle. The tert-butoxyl radical, a strong hydrogen atom abstractor, is representative of the hydroxyl (.cntdot.OH) and alkoxyl (.cntdot.OR) radicals; in contrast the DPPH radical, a much weaker radical, is a good kinetic model for hydroperoxyl (.cntdot.OOH) and peroxyl (.cntdot.OOR) radicals. These kinetic methods can be used to quant. assess the lability of drug candidates towards reaction with oxygen-centered radicals at an early stage of development and facilitate the design of inhibiting strategies.

IT **327037-01-4**, Statin IV
RL: PEP (Physical, engineering or chemical process); PRP (Properties); RCT (Reactant); PROC (Process)
(oxidn. of HMG-CoA reductase inhibitors by tert-butoxyl and 1,1-diphenyl-2-picrylhydrazyl radicals)

RN 327037-01-4 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16
REFERENCE(S):
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:757632 CAPLUS
DOCUMENT NUMBER: 134:50963
TITLE: In vitro evaluation of the disposition of a novel cysteine protease inhibitor
AUTHOR(S): Jacobsen, Wolfgang; Christians, Uwe; Benet, Leslie Z.
CORPORATE SOURCE: Department of Biopharmaceutical Sciences, School of Pharmacy, University of California, San Francisco, CA, 94143-0446, USA
SOURCE: Drug Metab. Dispos. (2000), 28(11), 1343-1351
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB K11777 (N-methyl-piperazine-Phe-homoPhe-vinylsulfone-phenyl) is a potent, irreversible cysteine protease inhibitor. Its therapeutic targets are cruzain, a cysteine protease of the protozoan parasite Trypanosoma cruzi, and cathepsins B and L, which are assocd. with cancer progression. The authors evaluated the metab. of K11777 by human liver microsomes, isolated cytochrome P 450 (CYP) enzymes, and flavin-contg. monooxygenase 3 (FMO3) in vitro. K11777 was metabolized by human liver microsomes to three major metabolites: N-oxide K11777 (apparent Km = 14.0 .mu.M and apparent Vmax = 3460 pmol .cntdot. mg-1 .cntdot. min-1), .beta.-hydroxy-homoPhe K11777 (Km = 16.8 .mu.M and Vmax = 1260 pmol .cntdot. mg-1 .cntdot. min-1), and N-desmethyl K11777 (Km = 18.3 .mu.M and Vmax = 2070 pmol .cntdot. mg-1 .cntdot. min-1). All three K11777 metabolites were formed by isolated CYP3A and their formation by human liver microsomes was inhibited by the

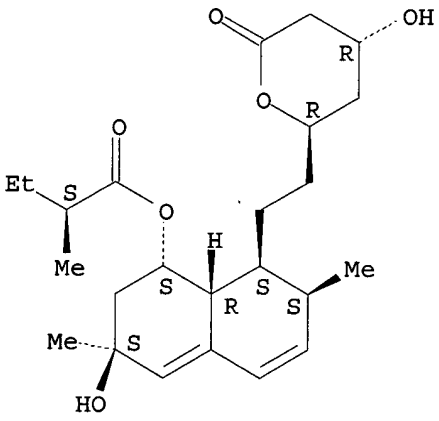
CYP3A inhibitor cyclosporine (50 .mu.M, 54-62% inhibition) and antibodies against human CYP3A4/5 (100 .mu.g of antibodies/100 .mu.g microsomal protein, 55-68% inhibition). CYP2D6 metabolized K11777 to its N-desmethyl metabolite with an apparent Km (9.2 .mu.M) lower than for CYP3A4 (25.0 .mu.M) and human liver microsomes. The apparent Km for N-oxide K11777 formation by cDNA-expressed FMO3 was 109 .mu.M. Based on the intrinsic formation clearances and the results of inhibition expts. (CYP2D6, 50 .mu.M bufuralol; FMO3 mediated, 100 mM methionine) using human liver microsomes, it was estd. that CYP3A contributes to >80% of K11777 metabolite formation. K11777 was a potent (IC50 = 0.06 .mu.M) and efficacious (max. inhibition 85%) NADPH-dependent inhibitor of human CYP3A4 mediated 6'.beta.-hydroxy lovastatin formation, suggesting that K11777 is not only a substrate but also a mechanism-based inhibitor of CYP3A4.

IT **125638-71-3**, 6'.beta.-Hydroxylovastatin
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(in vitro evaluation of disposition of a novel cysteine protease inhibitor by liver microsomes and cytochrome P 450 and flavin-contg. monooxygenase 3 in relation to inhibition of lovastatin metab.)

RN 125638-71-3 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 30
REFERENCE(S):
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(3) Chen, W; Curr Opin Cell Biol 1992, V4, P802 CAPLUS
(4) Coutts, R; J Pharmacol Toxicol Methods 1994, V31, P177 CAPLUS
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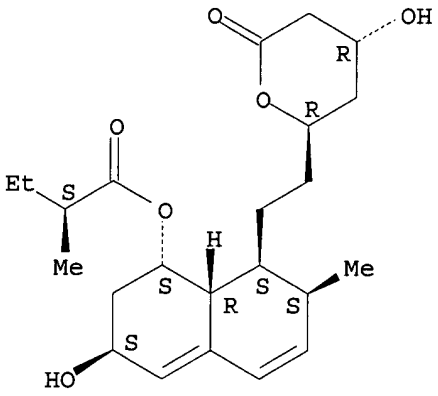
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 11 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:635998 CAPLUS
DOCUMENT NUMBER: 134:25095
TITLE: Quantitative determination of pravastatin and its biotransformation products in human serum by turbo ion

Golam Shameem

spray LC/MS/MS
AUTHOR(S): Mulvana, D.; Jemal, M.; Coates Pulver, S.
CORPORATE SOURCE: Advanced BioAnalytical Services, Ithaca, NY, 14850, USA
SOURCE: J. Pharm. Biomed. Anal. (2000), 23(5), 851-866
CODEN: JPBADA; ISSN: 0731-7085
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A sensitive, specific, accurate and reproducible anal. method was developed and validated to quantify pravastatin (Prav), pravastatin-d5 (Prav-d5), SQ-31906, SQ-31906-d5, and pravastatin lactone (Prav-Lac) in human serum samples. Serum samples (0.5 mL) were acidified and extd. by a solid-phase extn. procedure to isolate all five analytes from human serum. Sample exts. were reconstituted and analyzed by turbo ion spray liq. chromatog./tandem mass spectrometry (LC/MS/MS) in the pos. ion mode. The total run time was 9 min between injections. The assay demonstrated a lower limit of quantitation (LLQ) of 0.5 ng/mL for all five analytes. The calibration curves were linear from 0.5 ng/mL to 100 ng/mL for all five analytes. The coeffs. of detn. of all calibration curves were .gtoreq.0.999. Precision and accuracy quality control (QC) samples were prepd. at concns. of 2, 30, 80, and 500 ng/mL for all analytes. The intra-assay and inter-assay precision calcd. from QC samples were within 8% for all analytes. The inter-assay accuracy calcd. from QC samples was within 8% for all analytes. The extn. recoveries were .gtoreq.90% for all analytes. Benchtop stability expts. in an ice-water bath (.ltoreq.10) demonstrated that over time, Prav-Lac hydrolyzes to Prav in serum. Prav, Prav-d5, SQ-31906, and SQ-31906-d5 were stable under these conditions for up to 24 h. Hydrolysis was minimized by buffering the serum to pH 4.5 and maintaining the serum sample in an ice-water bath. All analytes were stable after three freeze/thaw cycles and in reconstitution soln. after 1 wk at 4. Stability of all analytes in human serum was demonstrated after storage at -70 for 77 days. The benchtop (.ltoreq.10) stability of pooled study samples was also investigated and the results were comparable to those obtained from serum QC samples.
IT **85956-22-5**, Pravastatin lactone
RL: ANT (Analyte); ANST (Analytical study)
(quant. detn. of pravastatin and its biotransformation products in human serum by turbo ion spray LC/MS/MS)
RN 85956-22-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 14
REFERENCE(S): (1) Everett, D; Drug Metab Dispos 1991, V19, P740 CAPLUS
(2) Funke, P; Biomed Environ Mass Spectrom 1989, V18, P904 CAPLUS
(3) Haria, M; Drugs 1997, V53, P299 CAPLUS
(4) Iacona, I; Ther Drug Monit 1994, V16, P191 CAPLUS
(5) Jemal, M; J Chromatogr B 1997, V693, P109 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

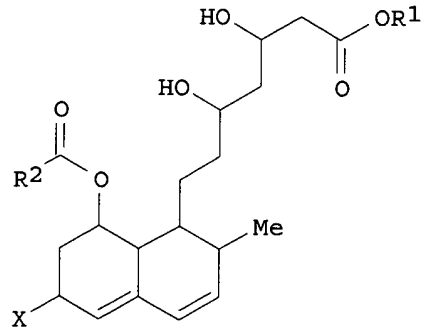
L7 ANSWER 12 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:535265 CAPLUS
DOCUMENT NUMBER: 133:134247
TITLE: Enzymatic production of HMG-CoA reductase inhibitors in microorganism with Bacillus hydroxylase
INVENTOR(S): Endo, Hirofumi; Yonetani, Yoshiyuki; Mizoguchi, Hiroshi; Hashimoto, Shin-ichi; Ozaki, Akio
PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan
SOURCE: PCT Int. Appl., 111 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000044886	A1	20000803	WO 2000-JP472	20000128
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1148122	A1	20011024	EP 2000-901980	20000128
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: JP 1999-21707 A 19990129
WO 2000-JP472 W 20000128
OTHER SOURCE(S): MARPAT 133:134247

Golam Shameem

GI



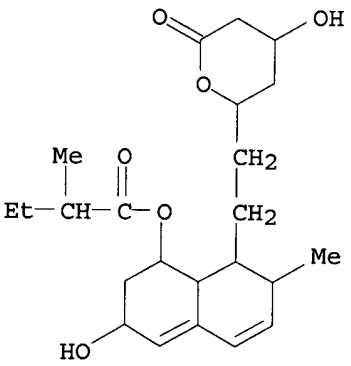
I

AB A protein originating in a microorganism belonging to the genus Bacillus having an activity of hydroxylating compds. represented by general formula I (R1 = H, (substituted)alkyl, alkali metal ion; R2 = (substituted)alkyl or -aryl; X = H), or lactones formed by cyclizing these compds., to form HMG-CoA reductase inhibitors II (I; R1,R2 as above; X = OH) or lactones of II; a DNA encoding this protein; and a recombinant DNA vector contg. this DNA are disclosed. A method of prodn. of compd. II or its lactone using the Bacillus hydroxylase is claimed. The microorganism does not form spores and has no hyphal growth. II may be useful for reducing/decreasing the serum cholesterol.

IT **81131-71-7P 85956-22-5P**
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(enzymic prodn. of HMG-CoA reductase inhibitors in microorganism with Bacillus hydroxylase)

RN 81131-71-7 CAPLUS

CN Butanoic acid, 2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

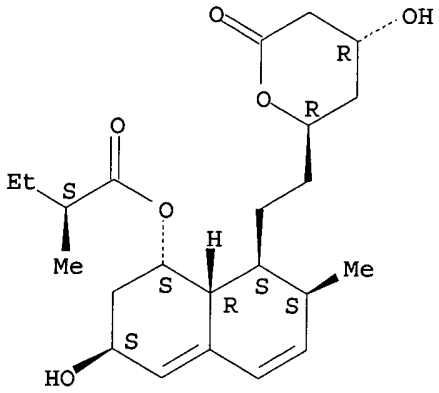


RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Golam Shameem



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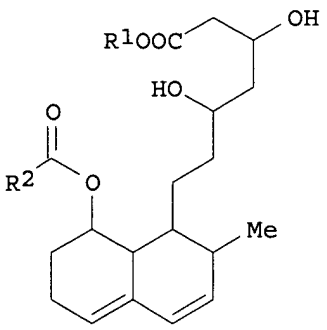
REFERENCE(S): (3) Bristol-Myers Squibb Company; JP 07-184670 A CAPLUS
(4) Bristol-Myers Squibb Company; CN 1106067 A CAPLUS
(5) Bristol-Myers Squibb Company; IL 111084 A CAPLUS
(6) Bristol-Myers Squibb Company; CA 2134025 A CAPLUS
(7) Bristol-Myers Squibb Company; HU 217104 B CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 13 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:513821 CAPLUS
DOCUMENT NUMBER: 133:103812
TITLE: Process for producing HMG-CoA reductase inhibitors
INVENTOR(S): Hashimoto, Shin-ichi; Yonetani, Yoshiyuki; Ozaki, Akio
PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000043533	A1	20000727	WO 2000-JP245	20000120
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1146126	A1	20011017	EP 2000-900832	20000120
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: JP 1999-12392 A 19990120
WO 2000-JP245 W 20000120
OTHER SOURCE(S): MARPAT 133:103812
GI



I

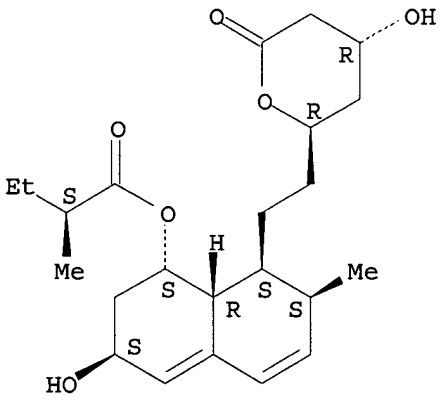
AB Compds. (I: R1 represents hydrogen, optionally substituted alkyl or an alkali metal; and R2 represents optionally substituted alkyl or optionally substituted aryl) or their lactones are incubated with microorganism that hydroxylates I or their lactones to manuf. HMG-CoA reductase inhibitors (II). The microorganism does not form spore and has no hyphal growth. II are useful for reducing/decreasing the serum cholesterol.

IT **85956-22-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(process for producing HMG-CoA reductase inhibitors)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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REFERENCE(S):
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(2) Gist-Brocades Bv; WO 9910499 A1 1999 CAPLUS
(3) Serizawa, N; Biotechnol Annu Rev 1996, V2, P373 CAPLUS

L7 ANSWER 14 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:255918 CAPLUS
DOCUMENT NUMBER: 133:83811
TITLE: Bioanalytical method validation design for the simultaneous quantitation of analytes that may undergo interconversion during analysis
AUTHOR(S): Jemal, M.; Xia, Y.-Q.

Golam Shameem

CORPORATE SOURCE: Metabolism and Pharmacokinetics, Bioanalytical Research, Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, NJ, USA
SOURCE: J. Pharm. Biomed. Anal. (2000), 22(5), 813-827
CODEN: JPBADA; ISSN: 0731-7085
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

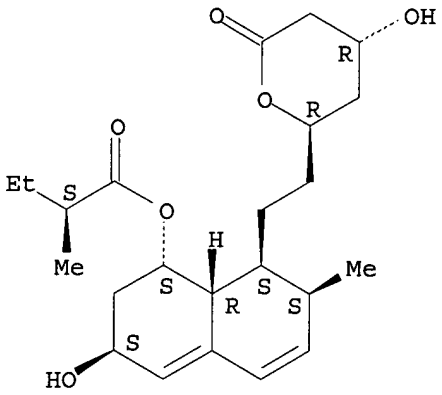
AB In the anal. of post-dose biol. samples for quant. detn. of two analytes that can potentially undergo interconversion, it is essential to minimize the interconversion during the multiple steps of the bioanal. method. However, even after optimizing the conditions of each step, some interconversion may be unavoidable. Even then, a method can be developed for the accurate simultaneous detn. of the two analytes in post-dose biol. samples if the compn., in terms of the ratio of the concns. of the two analytes, of the calibration stds. and quality control (QC) samples are selected judiciously, in relation to the compn. of the unknown samples to be analyzed. As an example of such interconverting analytes, a .delta.-hydroxy acid compd. (analyte 1) and its .delta.-lactone (analyte 2) were selected as model compds. that can potentially undergo interconversion. The effects of changing the relative concns. of the two analytes in QC samples vis-a-vis the calibration stds. on the performance of the method under conditions were investigated where: (a) the interconversion between the two analytes was minimized; (b) the conversion of analyte 2 to analyte 1 was enhanced; (c) the interconversion between the two analytes was enhanced. The results showed that the method performance, as measured by the accuracy and precision of the QC samples, was not acceptable when the ratio of concn. of analyte 1 to that of analyte 2 in the QC samples was different from that in the calibration stds. and the conditions used facilitated the conversion of one analyte to the other. However, when the relative concn. of the two analytes in the QC samples was identical to that of the calibration stds., the method performance was acceptable under all three conditions of interconversion. This was because the same degree of interconversion took place in the QC samples and calibration stds. The purpose of QC samples in bioanal. methods is to gauge how the method will perform for the anal. of post-dose test samples and hence, ideally, the relative concns. of the analytes in QC samples should be selected to mimic the anticipated concns. in the test samples. However, the relative concns. of the analytes in test samples may not be known a-priori, or may change from sample to sample; therefore, it is not always possible to construct QC samples that exactly mimic the relative concns. of analytes in the test samples. Thus, in order to cover the variety of test samples, the method should include, in addn. to QC samples that contain the analytes at the same relative concn. as in the calibration stds., QC samples with relative concns. that are different from those in the calibration stds., including those that contain only analyte 1 and only analyte 2. In addn., the conditions adopted for the method should favor the minimization of the conversion of the analyte that is expected to be the major component in the post-dose test samples.

IT **85956-22-5**, Pravastatin lactone
RL: ANT (Analyte); ANST (Analytical study)
(bioanal. method validation design for the simultaneous quantitation of analytes that may undergo interconversion during anal.)

RN 85956-22-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Golam Shameem



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REFERENCE(S):
(1) Carlucci, G; J Pharm Biomed Anal 1992, V10, P693 CAPLUS
(2) Gilbert, H; Methods Enzymol 1995, V251, P8 CAPLUS
(3) Jemal, M; Rapid Commun Mass Spectrom 1998, V12, P1389 CAPLUS
(4) Kantola, T; Clin Pharmacol Ther 1998, V64, P58 CAPLUS
(5) Kaufman, M; Int J Pharm 1990, V66, P97 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 15 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:210141 CAPLUS
DOCUMENT NUMBER: 132:241979
TITLE: Process for obtaining HMG-CoA reductase inhibitors of high purity
INVENTOR(S): Grahek, Rok; Milivojevic, Dusan; Bastarda, Andrej
PATENT ASSIGNEE(S): Lek Pharmaceutical and Chemical Company D.D., Slovenia
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000017182	A1	20000330	WO 1999-IB1553	19990917
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9955284	A1	20000410	AU 1999-55284	19990917
EP 1114040	A1	20010711	EP 1999-941797	19990917
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: SI 1998-241 A 19980918
WO 1999-IB1553 W 19990917

AB Lovastatin, pravastatin, simvastatin, mevastatin, atorvastatin, and

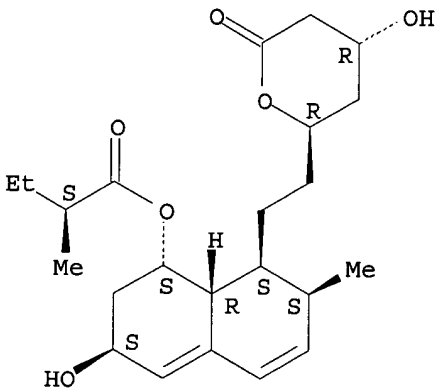
derivs. and analogs are known as HMG-CoA reductase inhibitors and are used as antihypercholesterolemic agents. The majority of them are produced by fermn. using microorganisms of different species identified as species belonging to Aspergillus, Monascus, Nocardia, Amycolatopsis, Mucor or Penicillium genus, some are obtained by treating the fermn. products using the method of chem. synthesis or they are the products of total chem. synthesis. The purity of the active ingredient is an important factor for manufg. the safe and effective pharmaceutical, esp. if the pharmaceutical product must be taken on a longer term basis in the treatment or prevention of high plasma cholesterol. The accumulation of the impurities from the pharmaceuticals of lower purity may cause many side effects during the medical treatment. The present invention relates to a new industrial process for the isolation of HMG-CoA reductase inhibitors using so-called displacement chromatog. Use of the invention enables to obtain HMG-CoA reductase inhibitors of high purity, with high yields, lower prodn. costs and suitable ecol. balance. Crude sodium salt of pravastatin (HPLC purity 88%) was dissolved in the mobile phase A (distd. water), pH was adjusted to 7 with 0.2M aq. NaOH soln. and filtered. The column was equilibrated with mobile phase A. The sample obtained in the above manner was fed onto the Grom-Sil 120-ODS HE column (particle size 30 11 .mu.m, column size 250 x 10 mm). The column was washed with the mobile phase B contg. 7% of diethylene glycol monobutyl ether in mobile phase A at the flow rate of 4.5 mL/min. Absorbance was measured at 260 nm, and the 0.5 mL fractions were collected with an initial increase in the absorbance. When the signal decreased the column was washed with 25 mL of 70% MeOH. The fractions obtained were analyzed by the HPLC method. The fractions with a purity 99.5% were pooled. In the pooled fractions (7 mL), the HPLC purity was 99.8%.

IT **85956-22-5P**, Pravastatin lactone
RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for obtaining HMG-CoA reductase inhibitors of high purity)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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(3) Merck & Co Inc; WO 9216276 A 1992 CAPLUS

Golam Shameem

(4) Monaghan, R; US 4231938 A 1980 CAPLUS
(5) Sclavo Spa; EP 0416416 A 1991 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

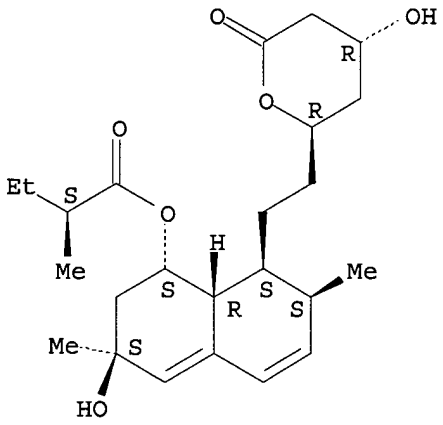
L7 ANSWER 16 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:165425 CAPLUS
DOCUMENT NUMBER: 133:53181
TITLE: Effect of multiple cilostazol doses on single-dose lovastatin pharmacokinetics in healthy volunteers
AUTHOR(S): Bramer, Steven L.; Brisson, Jerry; Corey, Alfred E.; Mallikaarjun, Suresh
CORPORATE SOURCE: Otsuka America Pharmaceutical, Inc., Rockville, MD, USA
SOURCE: Clin. Pharmacokinet. (1999), 37(Suppl. 2), 69-77
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Volunteers received single oral doses of 80 mg lovastatin on days 1, 7 and 9, as well as 100 mg oral cilostazol twice daily on days 2-8, followed by a single oral 150-mg cilostazol dose on day 9. Pharmacokinetic parameters were calcd. by using plasma concns. of lovastatin and its .beta.-hydroxy metabolite and of cilostazol and its metabolites. Differences in the pharmacokinetics of each drug when given alone or in combination were assessed by anal. of variance. The max. obsd. plasma concn. (Cmax) of lovastatin or its metabolite did not differ significantly when lovastatin was given alone and when it was given with 100 mg cilostazol. The mean ratios of the area under the plasma concn.-time curve from zero to the time of the last measurable concn. (AUCt) for lovastatin coadministered with 100 mg cilostazol to that with lovastatin given alone were 1.6 for lovastatin and 1.7 for its metabolite. With 150 mg cilostazol, lovastatin Cmax did not change, whereas Cmax of the metabolite increased 2.2-fold. The mean AUCt ratios for lovastatin given with 150 mg cilostazol/lovastatin given alone were 1.6 and 2.0 for lovastatin and its metabolite, resp. All the increases in lovastatin and metabolite AUC were significant, except for the 1.6-fold increase in lovastatin AUC with 150 mg cilostazol. Maximum steady-state plasma drug concn. and AUC during a dosage (AUCt) of 100 mg cilostazol twice daily decreased 14 and 15%, resp., upon lovastatin coadministration. Thus, exposure to lovastatin and its metabolite is increased by only .ltoreq.2-fold when cilostazol is coadministered, which is considerably less than that obsd. for potent cytochrome P 450 3A inhibitors such as itraconazole and grapefruit juice. Absorption of cilostazol decreased approx. 15% when it was given with lovastatin. No dosage adjustments are necessary for cilostazol when coadministered with lovastatin, whereas lovastatin dose redns. may be needed when the 2 drugs are given together.

IT **125638-71-3**
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(multiple cilostazol doses effect on single-dose lovastatin pharmacokinetics in humans in relation to formation of)

RN 125638-71-3 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 8
REFERENCE(S):
(1) Abbas, R; To be published in Hum Exp Toxicol
(2) Jusko, W; Applied pharmacokinetics -- principles of therapeutic drug monitoring 1986
(3) Kantola, T; Clin Pharmacol Ther 1998, V63(4), P397 CAPLUS
(6) Neuvonen, P; Clin Pharmacol Ther 1996, V60(1), P54 CAPLUS
(8) Transon, C; Eur J Clin Pharmacol 1996, V50(3), P209 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 17 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:758224 CAPLUS
DOCUMENT NUMBER: 132:185312
TITLE: Compatibility study of pravastatin sodium and pharmaceutical excipients
AUTHOR(S): Zyer, I.; Kerc, J.
CORPORATE SOURCE: Res. and Dev. Div., Lek Pharm. and Chem. Co. d.d, Ljubljana, Slovenia
SOURCE: Farm. Vestn. (Ljubljana) (1999), 50(Pos. Stev.), 300-301
CODEN: FMVTAV; ISSN: 0014-8229
PUBLISHER: Slovensko Farmacevtsko Drustvo
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The compatibility of pravastatin Na with a no. of commonly used tablet excipients was studied by using DSC and isothermal stability testing followed by HPLC anal. of related substances and degrdn. products. Sodium dihydrogen phosphate dihydrate with pH value of 4.5 and water content of 22.74% caused almost a complete degrdn. of pravastatin Na. The main degrdn. product was lactone form of pravastatin. Disodium hydrogen phosphate (DSHP) dihydrate includes about 20% of crystal water which appears to be uncrit. because the pH value was 9.2. Only a min. degrdn. was obsd. When using an anhyd. form of DSHP, no degrdn. of pravastatin sodium was established. Crystal water of sodium citrate dihydrate also did not effect the stability of pravastatin Na. Mg Al silicate with high water content of 7.1% causes a moderate degrdn. of pravastatin Na although its pH value was measured to be 10.2. Lactone was also found among other degrdn. products. Similar results were found for mixts. of pravastatin sodium with croscarmellose Na. A slight degrdn. was obsd. in binary mixts. of pravastatin with polacrilin K (Amberlite IRP 88), microcryst.

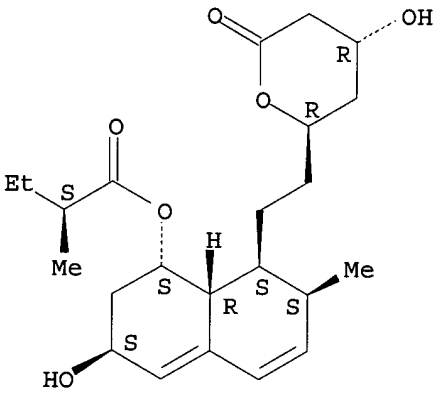
cellulose, Mg stearate, Aerosil 200 and yellow iron oxide. No interactions with pravastatin sodium were found for sodium lauryl sulfate, talc, hydroxypropyl cellulose, lactose and red iron oxide. Since interaction and incompatibility studies were carried out in 1:1 binary mixts. that is usually much higher ratio than the one in the tablet formulation, a small change in related substances and degrdn. products could be considered insignificant. The most crit. factors for incompatibility were found to be pH value and/or water content of excipients used in this study.

IT **85956-22-5**, Pravastatin lactone
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)
(compatibility of pravastatin sodium and tablet excipients)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 18 OF 69 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:753370 CAPLUS
DOCUMENT NUMBER: 132:2806
TITLE: New biotechnological process for preparing hydroxylated ML-236B derivatives, known as M-4 and M-4', and analogs thereof
INVENTOR(S): Kranjc, Sasо; Ivanc, Irena; Schauer, Manica
PATENT ASSIGNEE(S): Lek Pharmaceutical and Chemical Company D.D., Slovenia
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9960151	A1	19991125	WO 1999-IB923	19990521

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9937247 A1 19991206 AU 1999-37247 19990521

EP 1080220 A1 20010307 EP 1999-919467 19990521

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.: SI 1998-144 A 19980521

WO 1999-IB923 W 19990521

OTHER SOURCE(S): MARPAT 132:2806

AB The very effective conversion of ML-236B substances and derivs. thereof into 6'-hydroxylyted products with the microorganisms of species Amycolatopsis orientalis or with an ext. or a hydroxylation-effective enzyme derived from said microorganism, is described. The products obtained are suitable as HMG-CoA reductase inhibitors or intermediates thereof. Thus, the products can be used, for example, as an antihypercholesterolemic in pharmacy.

IT **85956-22-5P 85956-23-6P**

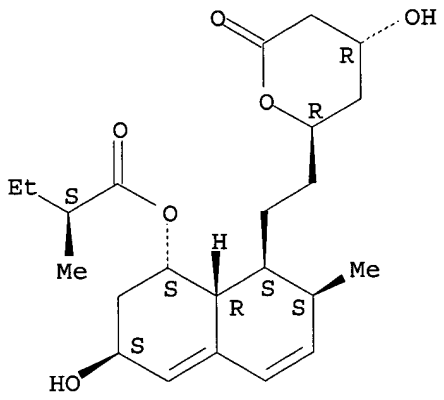
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)

(biotechnol. process for prepg. hydroxylated ML-236B derivs., known as M-4 and M-4', and analogs thereof)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

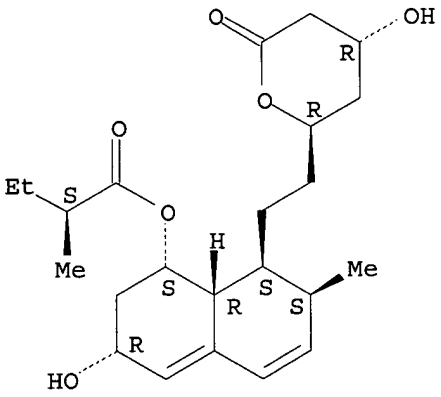
Absolute stereochemistry.



RN 85956-23-6 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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REFERENCE(S):
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(3) Sankyo Company Ltd; US 4346227 A 1982 CAPLUS
(4) Sankyo Company Ltd; US 4537859 A 1985 CAPLUS
(5) Sankyo Company Ltd; US 5153124 A 1992 CAPLUS

L7 ANSWER 19 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:632712 CAPLUS
DOCUMENT NUMBER: 132:93
TITLE: Small intestinal metabolism of the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor lovastatin and comparison with pravastatin
AUTHOR(S): Jacobsen, Wolfgang; Kirchner, Gabriele; Hallensleben, Katrin; Mancinelli, Laviero; Deters, Michael; Hackbarth, Ingelore; Baner, Karen; Benet, Leslie Z.; Sewing, Karl-Friedrich; Christians, Uwe
CORPORATE SOURCE: Department of Biopharmaceutical Sciences, School of Pharmacy, University of California, San Francisco, CA, USA
SOURCE: J. Pharmacol. Exp. Ther. (1999), 291(1), 131-139
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We compared the intestinal metab. of the structurally related 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors lovastatin and pravastatin in vitro. Human small intestinal microsomes metabolized lovastatin to its major metabolites 6'.beta.-hydroxy (apparent Km = 11.2.+-.3.3 .mu.M) and 6'-exomethylene (apparent Km = 22.7.+-.9.0 .mu.M) lovastatin. The apparent Km values were similar for lovastatin metab. by human liver microsomes. 6'.beta.-Hydroxylovastatin formation by pig small intestinal microsomes was inhibited with the following inhibition Ki values: cyclosporine, 3.3.+-.1.2 .mu.M; ketoconazole, 0.4.+-.0.1 .mu.M; and troleandomycin, 0.8.+-.0.9 .mu.M. Ki values for 6'-exomethylene lovastatin were similar. Incubation of pravastatin with human small intestinal microsomes resulted in the generation of 3'.alpha.,5'.beta.,6'.beta.-trihydroxypravastatin (apparent Km = 4560.+-.1410 .mu.M) and hydroxypravastatin (apparent Km = 5290.+-.1740 .mu.M). In addn., as in the liver, pravastatin was metabolized in the small intestine by sulfation and subsequent degrdn. to its main metabolite

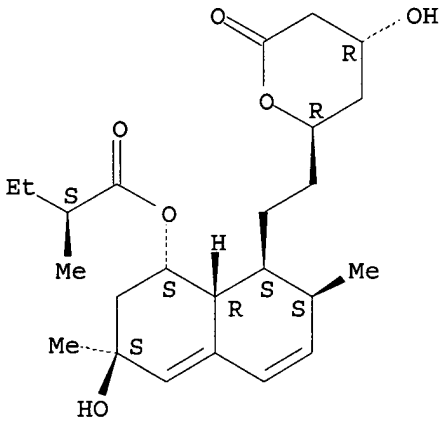
3'.alpha.-iso-pravastatin. It was concluded that lovastatin is metabolized by cytochrome P 450 3A enzymes in the small intestine. Compared with lovastatin, the cytochrome P 450-dependent intestinal intrinsic clearance of pravastatin was >5000-fold lower and cannot be expected to significantly affect its oral bioavailability or to be a significant site of drug interactions.

IT **125638-71-3**, 6'.beta.-Hydroxylovastatin
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(small intestinal metab. of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor lovastatin and comparison with pravastatin)

RN 125638-71-3 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 39
REFERENCE(S):
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(4) Estabrook, R; Methods Enzymol 1978, V52, P212 CAPLUS
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(6) Flint, O; Toxicol Appl Pharmacol 1997, V145, P99 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 20 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:587216 CAPLUS
DOCUMENT NUMBER: 131:346095
TITLE: Grapefruit juice increases serum concentrations of atorvastatin and has no effect on pravastatin
AUTHOR(S): Lilja, Jari J.; Kivisto, Kari T.; Neuvonen, Pertti J.
CORPORATE SOURCE: Department of Clinical Pharmacology, University of Helsinki and Helsinki University Central Hospital, Helsinki, FIN-00290, Finland
SOURCE: Clin. Pharmacol. Ther. (St. Louis) (1999), 66(2), 118-127
CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal

Golam Shameem

LANGUAGE: English

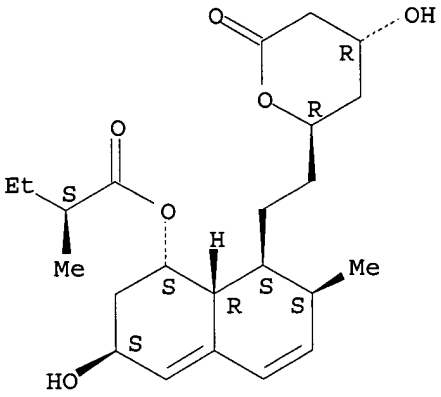
AB Background: Grapefruit juice greatly increases the bioavailability of lovastatin and simvastatin. We studied the effect of grapefruit juice on the pharmacokinetics of atorvastatin and pravastatin. Methods: Two randomized, two-phase crossover studies were performed; study I with atorvastatin in 12 healthy volunteers and study II with pravastatin in 11 healthy volunteers. In both studies, volunteers took 200 mL double-strength grapefruit juice or water three times a day for 2 days. On day 3, each subject ingested a single 40 mg dose of atorvastatin (study I) or pravastatin (study II) with either 200 mL grape-fruit juice or water, and an addnl. 200 mL was ingested 1/2 h and 1 1/2 h later. In addn., subjects took 200 mL grapefruit juice or water three times a day on days 4 and 5 in study I. In study I, serum concns. of atorvastatin acid, atorvastatin lactone, 2-hydroxyatorvastatin acid, 2-hydroxyatorvastatin lactone, and active and total 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitors were measured up to 72 h. In study II, pravastatin, pravastatin lactone, and active and total HMG-CoA reductase inhibitors were measured up to 24 h. Results: Grapefruit juice increased the area under the serum concn.-time curve of atorvastatin acid from time zero to 72 h [AUC(0-72)] 2.5-fold ($P < .01$), whereas the peak serum concn. (Cmax) was not significantly changed. The time of the peak concn. (tmax) and the elimination half-life (t1/2) of atorvastatin acid were increased ($P < .01$). The AUC(0-72) of atorvastatin lactone was increased 3.3-fold ($P < .01$) and the Cmax 2.6-fold ($P < .01$) by grapefruit juice, and the tmax and t1/2 were also increased ($P < .05$). Grapefruit juice decreased the Cmax ($P < .001$) and AUC(0-72) ($P < .001$) of 2-hydroxyatorvastatin acid and increased its tmax and t1/2 ($P < .01$). Grapefruit juice also decreased the Cmax ($P < .001$) and AUC(0-72) ($P < .05$) of 2-hydroxyatorvastatin lactone. The AUC(0-72) values of active and total HMG-CoA reductase inhibitors were increased 1.3-fold ($P < .05$) and 1.5-fold ($P < .01$), resp., by grapefruit juice. In study II, the only significant change obsd. in the pharmacokinetics of pravastatin was prolongation of the tmax of active HMG-CoA reductase inhibitors by grapefruit juice ($P < .05$). Conclusions: Grapefruit juice significantly increased serum concns. of atorvastatin acid, atorvastatin lactone, and active and total HMG-CoA reductase inhibitors, probably by decreasing CYP3A4-mediated first-pass metab. of atorvastatin in the small intestine. On the other hand, grapefruit juice had no effect on the pharmacokinetics of pravastatin. Concomitant use of atorvastatin and at least large amts. of grapefruit juice should be avoided, or the dose of atorvastatin should be reduced accordingly.

IT **85956-22-5**, Pravastatin lactone
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(grapefruit juice increases serum concns. of atorvastatin and has no effect on pravastatin)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 24
REFERENCE(S):
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(7) Haria, M; Drugs 1997, V53, P299 CAPLUS
(9) Jacobsen, W; Drug Metab Dispos 1999, V27, P173 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 21 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:313328 CAPLUS
DOCUMENT NUMBER: 131:120749
TITLE: Selection of Solid Dosage Form Composition through Drug-Excipient Compatibility Testing
AUTHOR(S): Serajuddin, Abu T. M.; Thakur, Ajit B.; Ghoshal, Rabin N.; Fakes, Michael G.; Ranadive, Sunanda A.; Morris, Kenneth R.; Varia, Sailesh A.
CORPORATE SOURCE: Pharmaceutics R&D Department, Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, NJ, 08903, USA
SOURCE: J. Pharm. Sci. (1999), 88(7), 696-704
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A drug-excipient compatibility screening model was developed by which potential stability problems due to interactions of drug substances with excipients in solid dosage forms can be predicted. The model involved storing drug-excipient blends with 20% added water in closed glass vials at 50.degree. and analyzing them after 1 and 3 wk for chem. and phys. stability. The total wt. of drug-excipient blend in a vial was usually kept at about 200 mg. The amt. of drug substance in a blend was detd. on the basis of the expected drug-to-excipient ratio in the final formulation. Potential roles of several key factors, such as the chem. nature of the excipient, drug-to-excipient ratio, moisture, microenvironmental pH of the drug-excipient mixt., temp., and light, on dosage form stability could be identified by using the model. Certain phys. changes, such as polymorphic conversion or change from cryst. to amorphous form, that could occur in drug-excipient mixts. were also studied. Selection of dosage form compn. by using this model at the

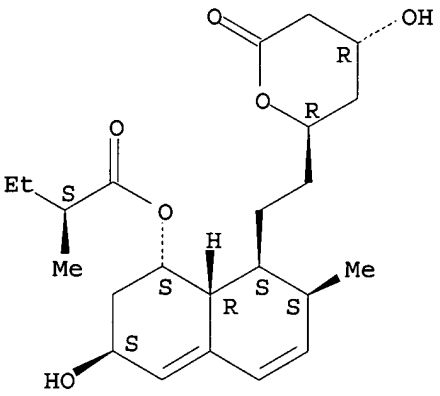
outset of a drug development program would lead to redn. of "surprise" problems during long-term stability testing of drug products.

IT **85956-22-5**
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative) (selection of solid dosage form compn. through drug-excipient compatibility testing)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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(10) Gu, L; Pharm Res 1990, V7, P379 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 22 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:172494 CAPLUS
DOCUMENT NUMBER: 130:305996
TITLE: Comparison of cytochrome P-450-dependent metabolism and drug interactions of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors lovastatin and pravastatin in the liver
AUTHOR(S): Jacobsen, Wolfgang; Kirchner, Gabriele; Hallensleben, Katrin; Mancinelli, Laviero; Deters, Michael; Hackbarth, Ingelore; Benet, Leslie Z.; Sewing, Karl-Fr.; Christians, Uwe
CORPORATE SOURCE: Department of Biopharmaceutical Sciences, School of Pharmacy, University of California at San Francisco, San Francisco, CA, 94143-0446, USA
SOURCE: Drug Metab. Dispos. (1999), 27(2), 173-179
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In an in vitro study, the cytochrome P 450 3A (CYP3A)-dependent metab. and drug interactions of the 3-hydroxy-3-methylglutaryl-Co A reductase

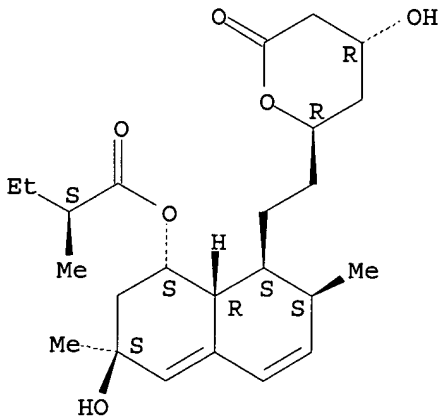
inhibitors lovastatin and pravastatin were compared. Lovastatin was metabolized by human liver microsomes to two major metabolites: 6'.beta.-hydroxy [Michaelis-Menten const. (Km): 7.8 .+-. 2.7 .mu.M] and 6'-exomethylene lovastatin (Km, 10.3 .+-. 2.6 .mu.M). 6'.beta.-Hydroxylovastatin formation in the liver was inhibited by the specific CYP3A inhibitors cyclosporine (Ki, 7.6 .+-. 2.3 .mu.M), ketoconazole (Ki, 0.25 .+-. 0.2 .mu.M), and troleandomycin (Ki, 26.6 .+-. 18.5 .mu.M). Incubation of pravastatin with human liver microsomes resulted in the generation of 3' .alpha.,5' .beta.,6' .beta.-trihydroxy pravastatin (Km, 4,887 .+-. 2,185 .mu.M) and hydroxy pravastatin (Km, 20,987 .+-. 9,389 .mu.M). The formation rates of 3' .alpha.,5' .beta.,6' .beta.-trihydroxy pravastatin by reconstituted CYP3A enzymes were (1,000 .mu.M pravastatin) 1.9 .+-. 0.6 pmol.cntdot.min-1.cntdot.pmol CYP3A4 and 0.06 .+-. 0.04 pmol.cntdot.min-1.cntdot.pmol CYP3A5, and the formation rates of hydroxy pravastatin were 0.12 .+-. 0.02 pmol.cntdot.min-1.cntdot.pmol CYP3A4 and 0.02 .+-. 0.004 pmol.cntdot.min-1.cntdot.pmol CYP3A5. The specific CYP3A inhibitors cyclosporine, ketoconazole, and troleandomycin significantly inhibited hydroxy pravastatin formation by human liver microsomes, but only ketoconazole inhibited 3' .alpha.,5' .beta.,6' .beta.-trihydroxy pravastatin formation, suggesting that other CYP enzymes are involved in its formation. It is concluded that, compared with lovastatin [CLint formation 6' .beta.-hydroxylovastatin (.mu.l.cntdot.min-1.cntdot.mg-1): 199 .+-. 248, 6'- exomethylene lovastatin: 138 .+-. 104], CYP3A-dependent metab. of pravastatin [CLint formation 3' .alpha.,5' .beta.,6' .beta.-trihydroxy pravastatin (.mu.l.cntdot.min-1.cntdot.mg-1): 0.03 .+-. 0.03 and hydroxy pravastatin: 0.02 .+-. 0.02] is a minor elimination pathway. In contrast to lovastatin, drug interactions with pravastatin CYP3A-catalyzed metab. cannot be expected to have a clin. significant effect on its pharmacokinetics.

IT **125638-71-3**
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(cytochrome P 450-dependent metab. and drug interactions of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors lovastatin and pravastatin in the liver)

RN 125638-71-3 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



Golam Shameem

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REFERENCE(S): (1) Anderson, K; J Am Med Assoc 1987, V257, P2176 CAPLUS
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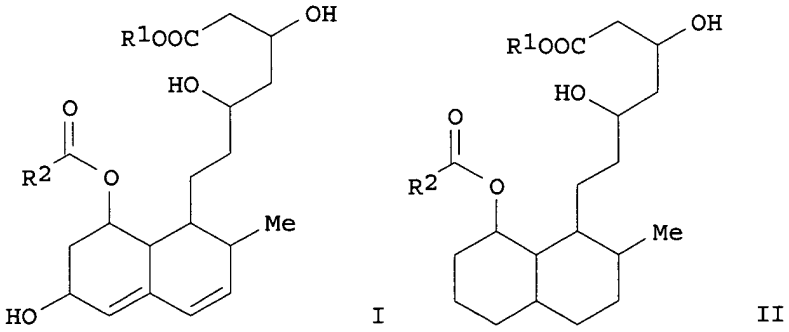
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 23 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:127041 CAPLUS
DOCUMENT NUMBER: 130:167251
TITLE: Process for the preparation of HMG-CoA reductase inhibitors
INVENTOR(S): Takano, Yutaka; Hasegawa, Masaru; Mori, Hideo; Ando, Katsuhiko; Ochiai, Keiko; Motoyama, Hiroaki; Ozaki, Akio
PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9907872	A1	19990218	WO 1998-JP3396	19980730
W: AU, BG, BR, CA, CN, CZ, HU, IL, JP, KR, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9884606	A1	19990301	AU 1998-84606	19980730
EP 1020530	A1	20000719	EP 1998-935282	19980730
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6245535	B1	20010612	US 2000-463912	20000202
PRIORITY APPLN. INFO.:			JP 1997-213636 A	19970807
			WO 1998-JP3396 W	19980730

OTHER SOURCE(S): MARPAT 130:167251
GI



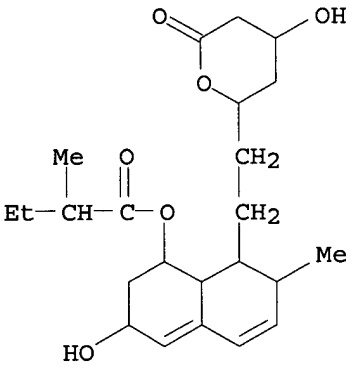
Golam Shameem

AB A process for the prepn. of compds. represented by general formula (II-a) (I: wherein R1 is hydrogen, optionally substituted alkyl or alkali metal; and R2 is optionally substituted alkyl or aryl) or lactones (II-b) derived therefrom through ring closure, which comprises incubation a compd. represented by general formula (I-a) (II: wherein R1 and R2 are each as described above) or a lactone (I-b) derived therefrom through ring closure with Bacillus or an enzyme having the activity of forming the compds. I or lactone from the compds. II or lactone in a reaction fluid to form the compd. I or lactone in the reaction fluid, and recovering the compd. I or lactone from the reaction fluid. These HMG-CoA reductase inhibitors are useful for reducing serum cholesterol level.

IT **81131-71-7P 85956-22-5P**
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(process for prepn. of HMG-CoA reductase inhibitors)

RN 81131-71-7 CAPLUS

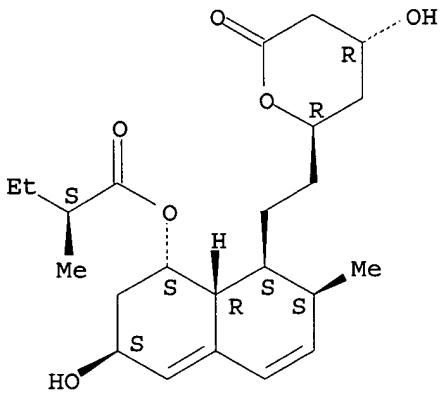
CN Butanoic acid, 2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)



RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3

Golam Shameem

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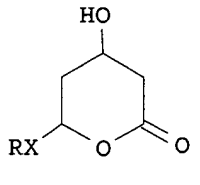
(3) Young Jin Pharmaceutical Ind Co, Ltd; WO 98/06867 A 1998 CAPLUS

L7 ANSWER 24 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:682331 CAPLUS
DOCUMENT NUMBER: 129:290016
TITLE: Chromatographic enantiomer separation of lactones with N-(acryloyl)-L-phenylalanine D-neomenthylamide modified polymers
INVENTOR(S): Bomer, Bruno; Grosser, Rolf; Kohler, Burkhard; Michel, Stefan; Zweering, Uwe
PATENT ASSIGNEE(S): Bayer Aktiengesellschaft, Germany; Bomer, Karin-Elfriede; Bomer, Guido, Martin; Bomer, Felix, Marcel +hm; Lange, Walter
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

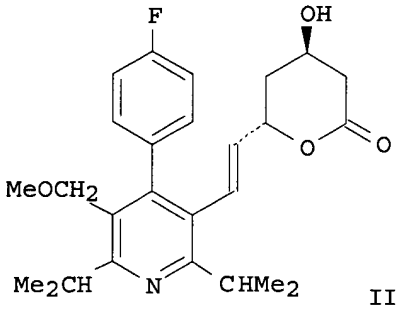
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9845230	A1	19981015	WO 1998-EP1788	19980326
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
DE 19714343	A1	19981015	DE 1997-19714343	19970408
AU 9872112	A1	19981030	AU 1998-72112	19980326
EP 973705	A1	20000126	EP 1998-919159	19980326
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001521507	T2	20011106	JP 1998-542317	19980326
ZA 9802948	A	19981009	ZA 1998-2948	19980407
US 6274736	B1	20010814	US 1999-380332	19990903

PRIORITY APPLN. INFO.: DE 1997-19714343 A 19970408
WO 1998-EP1788 W 19980326

OTHER SOURCE(S): MARPAT 129:290016
GI



I



II

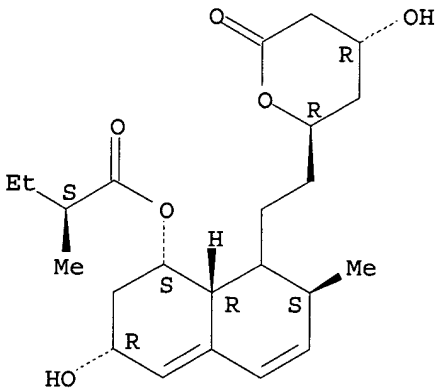
AB The present invention describes the use of optically active polymers made from N-(acryloyl)-(S)-phenylalanine D-neomenthylamide or its enantiomer, in cross-linked form and/or bonded to a carrier, as stationary phases for chromatog. enantiomer sepn. of lactones I (R = org. residue; X = CH2CH2, CH:CH). Thus, racemic II was sepd. (enantioselectivity .alpha. = 5.82) using silica gel modified with N-(acryloyl)phenylalanine D-neomenthylamide.

IT **213910-82-8P**
RL: PUR (Purification or recovery); PREP (Preparation)
(chromatog. enantiomer sepn. of lactones with N-(acryloyl)-L-phenylalanine D-neomenthylamide modified polymers)

RN 213910-82-8 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3R,7S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 25 OF 69 CAPLUS COPYRIGHT 2001 ACS

Golam Shameem

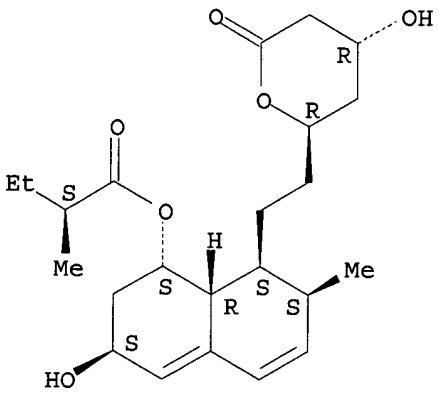
ACCESSION NUMBER: 1997:772128 CAPLUS
DOCUMENT NUMBER: 128:110317
TITLE: Metabolism of pravastatin sodium by 3.alpha.-hydroxysteroid dehydrogenase
AUTHOR(S): Muramatsu, Shigeki; Komokata, Yuko; Tanaka, Yorihisa; Takahagi, Hidekuni
CORPORATE SOURCE: Analytical and Metabolic Research Laboratories, Sankyo Co., Ltd., Tokyo, 140, Japan
SOURCE: Biol. Pharm. Bull. (1997), 20(11), 1199-1203
CODEN: BPBLEO; ISSN: 0918-6158
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English

AB When incubated with isolated rat hepatocytes, pravastatin sodium (PS) yielded a small amt. of a metabolite in addn. to two major metabolites that have already been reported. The previously uncharacterized metabolite was found to be formed by at first being enzymically dehydrogenated to 6'-keto intermediate (R-104), followed by decompn. to give the aromatized metabolite (R-195), through spontaneous deesterification with accompanying aromatization. The PS-6' .beta.-hydroxydehydrogenase activity was localized in cytosolic fraction and required NADP, preferentially over NAD, as a cofactor. The formation of R-195 by rat liver cytosol was strongly inhibited by indomethacin, 3.alpha.-hydroxysteroids (but not 3.beta.-isomers) and 3-ketosteroids. The results and high substrate specificity of purified PS-6'.beta.-hydroxydehydrogenase toward 3.alpha.-hydroxysteroids suggested that the enzyme is identical to 3.alpha.-hydroxysteroid dehydrogenase.

IT **85956-22-5**, R 414
RL: RCT (Reactant)
(metab. of pravastatin sodium by 3.alpha.-hydroxysteroid dehydrogenase in hepatocytes)

RN 85956-22-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

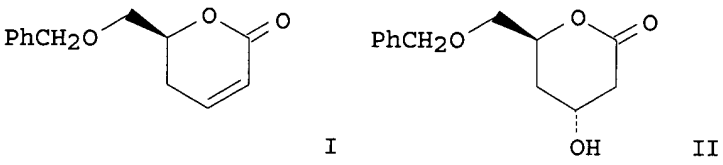
Absolute stereochemistry.



L7 ANSWER 26 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:303145 CAPLUS
DOCUMENT NUMBER: 127:50445
TITLE: A facile asymmetric synthesis of the compactin lactone moiety

Golam Shameem

AUTHOR(S): Schabbert, Silke; Tiedemann, Ralf; Schaumann, Ernst
CORPORATE SOURCE: Inst. Organische Chem., Technische Univ. Clausthal, Clausthal-Zellerfeld, D-38678, Germany
SOURCE: Liebigs Ann./Recl. (1997), (5), 879-880
CODEN: LIARFV
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 127:50445
GI



I II

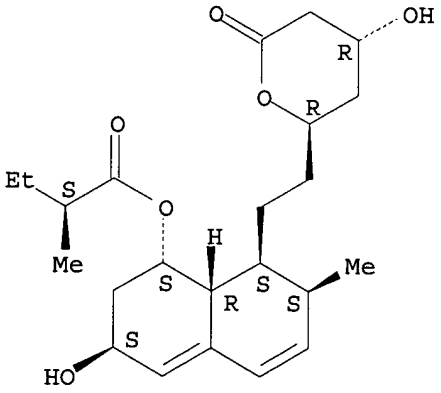
AB Starting from (R)-O-benzylglycidol and the S-stabilized allyl anion of MeOCH2CH:CHSPh, a [3+3] synthesis of the .alpha.,.beta.-unsatd. (6S)-.delta.-lactone I is achieved. Subsequent diastereoselective addn. of PhMe2SiMeCuLi and unmasking of the latent OH function provides the lactone unit II of compactin.

IT **85956-22-5P**, (+)-Pravastatin lactone
RL: PNU (Preparation, unclassified); PREP (Preparation)
(asym. synthesis of a pravastatin lactone precursor)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

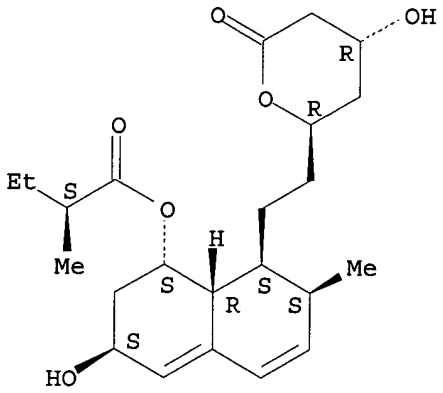
Absolute stereochemistry.



L7 ANSWER 27 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:704883 CAPLUS
DOCUMENT NUMBER: 126:114865
TITLE: Liquid chromatographic determination of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors
AUTHOR(S): Shen, Pei-Ming; Shiao, Ming-Shi; Chung, Huey-Ru; Lee, Golam Shameem

Kuan-Rong; Chao, Yu-Sheng; Hunt, Vincent M.
CORPORATE SOURCE: Dep. Med. Research Education, Veterans General Hosp., Taipei, 11217, Taiwan
SOURCE: J. Chin. Chem. Soc. (Taipei) (1996), 43(5), 451-457
CODEN: JCCTAC; ISSN: 0009-4536
PUBLISHER: Chinese Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Reversed-phase high-performance liq. chromatog. (RP-HPLC) was used as a tool to explore the retention behavior and sepn. of four 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitors, namely compactin, lovastatin, simvastatin, and pravastatin in their hydroxy acid and lactone forms. The contribution of C-6 and C-2' Me groups and lactonization to the mol. hydrophobicity among these 4 structurally related HMG-CoA reductase inhibitors were elucidated. Eight components (four lactones and four hydroxy acids) could be resolved by RP-HPLC with isocratic elution. In a binary mobile phase system of acetonitrile-water contg. 0.5% acetic acid, the free hydroxy acids and corresponding lactose forms remained intact and were completely sepd. This study demonstrated that RP-HPLC is suitable for simultaneous detn. of active and prodrug forms of these HMG-CoA reductase inhibitors.
IT **85956-22-5**, Pravastatin lactone
RL: ANT (Analyte); ANST (Analytical study)
(liq. chromatog. detn. of 3-hydroxy-3-methylglutaryl CoA reductase inhibitors)
RN 85956-22-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 28 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:981713 CAPLUS
DOCUMENT NUMBER: 124:135103
TITLE: 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors: oxime ether analogs of pravastatin
AUTHOR(S): Turabi, Noor; DiPietro, Richard A.; Mantha, Subbarao; Ciosek, Carl; Rich, Lois; Tu, Jan-I.
CORPORATE SOURCE: Diagnostics Drug Discovery, Bristol-Myers Squibb Pharmaceutical Res. Inst., Princeton, NJ, 08543-4000, USA

Golam Shameem

SOURCE: Bioorg. Med. Chem. (1995), 3(11), 1479-84
CODEN: BMECEP; ISSN: 0968-0896
DOCUMENT TYPE: Journal
LANGUAGE: English

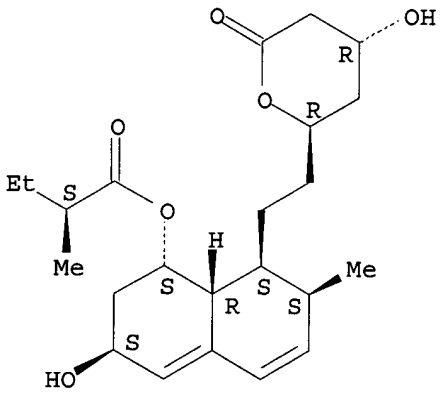
AB Pravastatin, a potent anti-hypercholesteremic drug, was developed by Bristol-Myers Squibb for treatment of hypercholesterolemia and other related diseases. Several structurally related compds. (SQ 31554, SQ 31879, SQ 31947, SQ 32391, SQ 32770, SQ 32390 and SQ 32469) modified at the 3-position of the hexahydronaphthalene ring system of pravastatin were prepd. in the course of developing the basic reagents for a RIA of the parent drug. The biol. activity of these analogs was comparable to pravastatin itself. Indeed, one member of this series was several-fold more potent than pravastatin.

IT **85956-22-5P**, SQ 31369
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(in prepn. of pravastatin analogs as hydroxymethylglutaryl-CoA reductase inhibitors)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 29 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:444033 CAPLUS
DOCUMENT NUMBER: 122:213765
TITLE: Preparation of hexahydronaphthalene ester derivatives, as anticholesteremics
INVENTOR(S): Ishihara, Sadao; Kogen, Hiroshi; Koga, Teiichiro; Kitazawa, Eiichi; Serizawa, Nobufusa
PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 173 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 609058	A2	19940803	EP 1994-300557	19940126
EP 609058	A3	19950419		

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EP 609058	B1	19981209			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
IL 108432	A1	19970930	IL 1994-108432	19940125	
ZA 9400548	A	19940829	ZA 1994-548	19940126	
AT 174324	E	19981215	AT 1994-300557	19940126	
ES 2126057	T3	19990316	ES 1994-300557	19940126	
CZ 285658	B6	19991013	CZ 1994-186	19940127	
CA 2114450	AA	19940730	CA 1994-2114450	19940128	
NO 9400309	A	19940801	NO 1994-309	19940128	
AU 9454728	A1	19940804	AU 1994-54728	19940128	
AU 664323	B2	19951109			
FI 9400424	A	19941107	FI 1994-424	19940128	
HU 67740	A2	19950428	HU 1994-242	19940128	
RU 2114101	C1	19980627	RU 1994-2313	19940128	
TW 411337	B	20001111	TW 1994-83100729	19940128	
CN 1098099	A	19950201	CN 1994-102611	19940129	
CN 1070487	B	20010905			
JP 06279280	A2	19941004	JP 1994-9771	19940131	
US 5491167	A	19960213	US 1994-189040	19940131	

PRIORITY APPLN. INFO.: JP 1993-13063 A 19930129

OTHER SOURCE(S): MARPAT 122:213765

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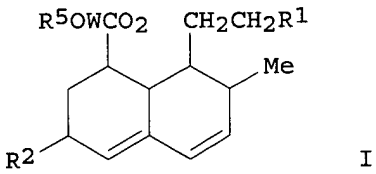
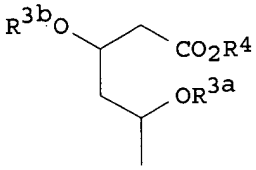
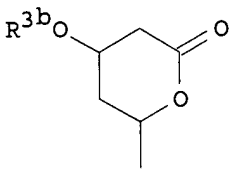


I



II



III

AB Title compds. I (R1 = II, III; R2 = H, R3O wherein R3, R3a, R3b are = H, hydroxy-protecting group, C1-6 alkyl, (halo) C1-6 alkylsulfonyl, (substituted) C6-14 arylsulfonyl; R4 = H, carboxy-protecting group; R5 = C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, (substituted) C6-14 aryl, (substituted)C6-14 aryl-C1-6 alkyl, a fused polycyclyl; W = (substituted) C1-6 alkylene) and their salts and esters thereof, are prepd. (2RS)-2-(4-methylphenoxy)butyric acid, Et3N and ClP(O)(OEt)2 were added to (4R,6R)-6-[(1S,2S,6S,8S,8aR)-2-[1,2,6,7,8,8a-hexahydro-6-tert-butyldimethylsilyloxy-8-hydroxy-2-methyl-1-naphthyl]ethyl]tetrahydro-4-tert-butyldimethylsilyloxy-2H-pyran-2-one (prepn. given) to give after workup the appropriate 2R- and 2S-butyryloxy deriv. which were deprotected and treated with 0.1N aq. NaOH to give the title compd. Na (3R,5R)-3,5-dihydroxy-7-[(1S,2S,6S,8S,8aR)-1,2,6,7,8,8a-hexahydro-6-hydroxy-8-[(2RS)-2-(4-methylphenoxy)butyryloxy]-2-methyl-1-naphthyl]heptanoate which when tested for inhibition of biosynthesis of cholesterol using HMG-CoA showed an IC50 of 30.9 nM vs. a prior art compd. which was 44.9 nM. Pharmaceutical formulations comprising I are given.

IT **161788-27-8P 161788-30-3P 161788-33-6P**
161788-36-9P 161788-39-2P 161788-42-7P

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161788-45-0P 161788-48-3P 161788-51-8P
161788-54-1P 161788-57-4P 161788-60-9P
161788-63-2P 161788-66-5P 161788-69-8P
161788-72-3P 161788-75-6P 161788-78-9P
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161904-06-9P 161904-09-2P 161904-12-7P
161904-15-0P 161904-18-3P 161904-21-8P
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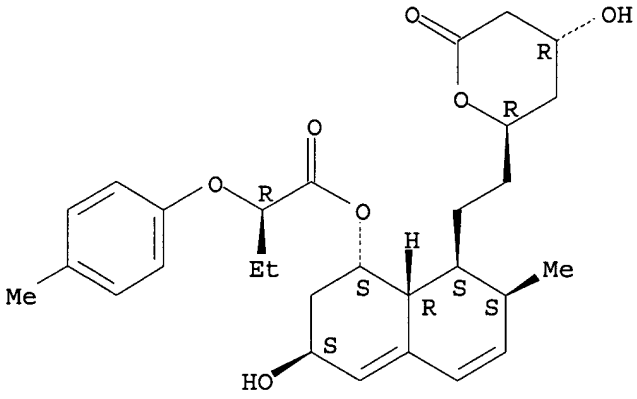
161904-33-2P 161904-36-5P 161904-38-7P
161904-40-1P 161904-43-4P 161904-46-7P
161904-49-0P 161904-52-5P 161904-55-8P
161904-58-1P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of hexahydronaphthalene ester derivs. as anticholesteremics)

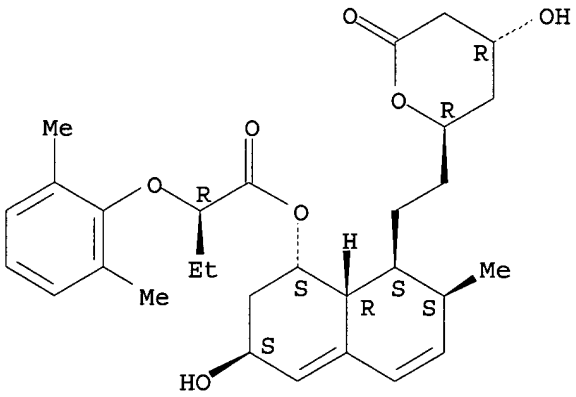
RN 161788-27-8 CAPLUS
CN Butanoic acid, 2-(4-methylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



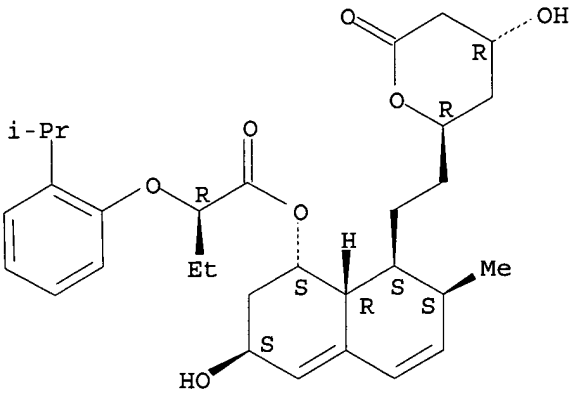
RN 161788-30-3 CAPLUS
CN Butanoic acid, 2-(2,6-dimethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



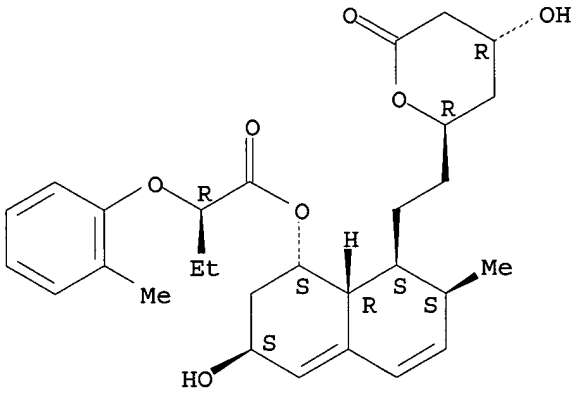
RN 161788-33-6 CAPLUS
CN Butanoic acid, 2-[2-(1-methylethyl)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



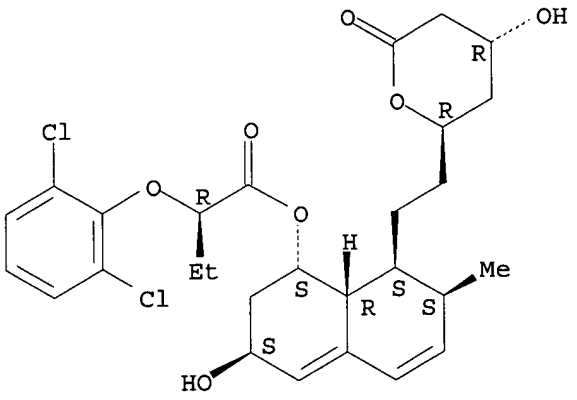
RN 161788-36-9 CAPLUS
CN Butanoic acid, 2-(2-methylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



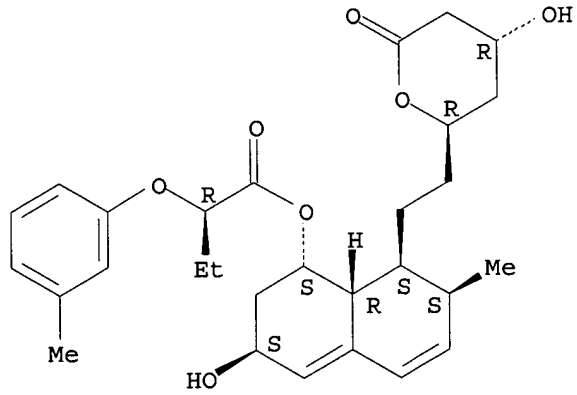
RN 161788-39-2 CAPLUS
CN Butanoic acid, 2-(2,6-dichlorophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



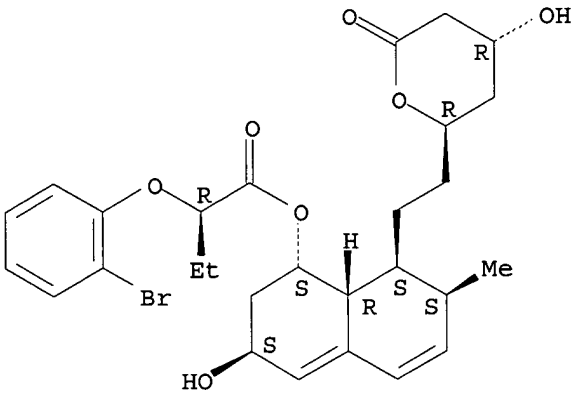
RN 161788-42-7 CAPLUS
CN Butanoic acid, 2-(3-methylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



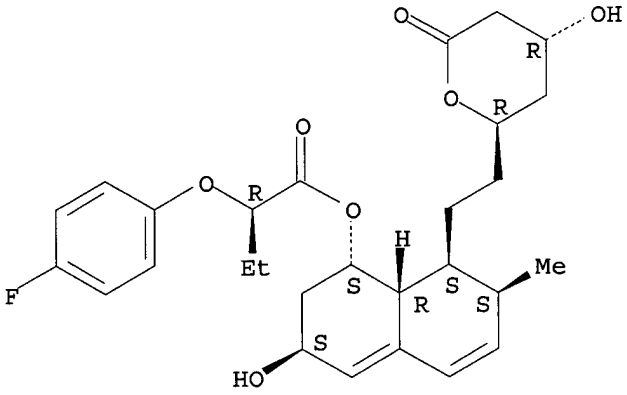
RN 161788-45-0 CAPLUS
CN Butanoic acid, 2-(2-bromophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



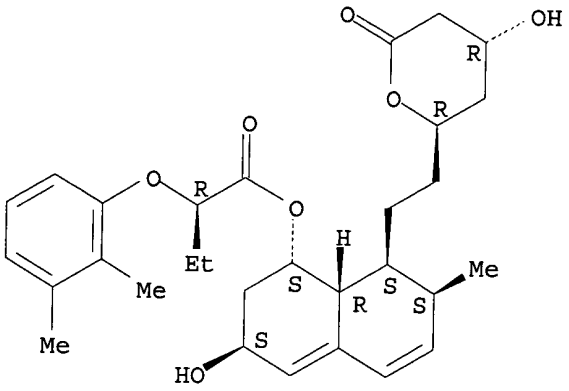
RN 161788-48-3 CAPLUS
CN Butanoic acid, 2-(4-fluorophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



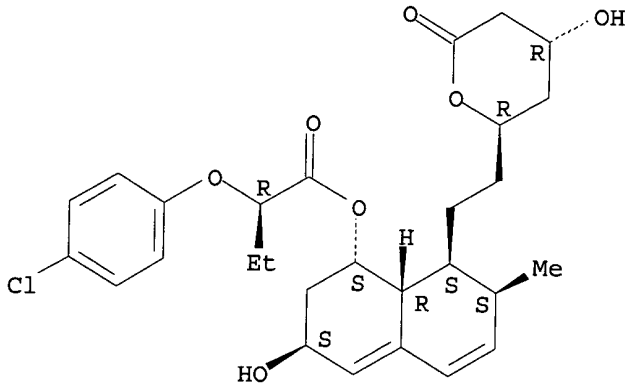
RN 161788-51-8 CAPLUS
CN Butanoic acid, 2-(2,3-dimethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



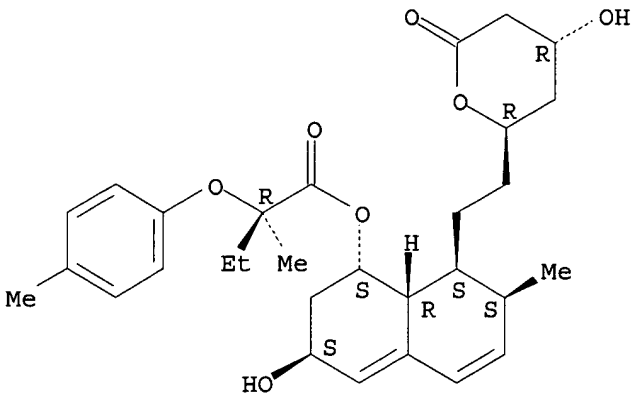
RN 161788-54-1 CAPLUS
CN Butanoic acid, 2-(4-chlorophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



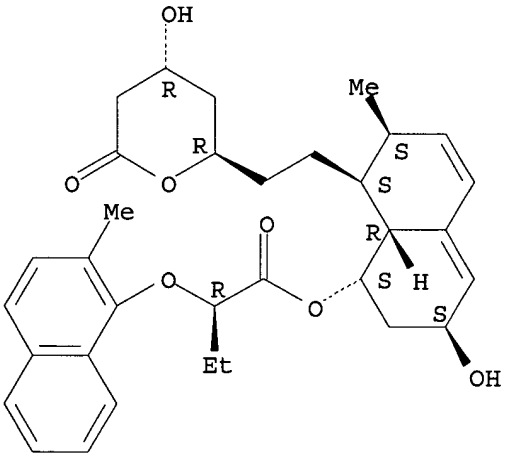
RN 161788-57-4 CAPLUS
CN Butanoic acid, 2-methyl-2-(4-methylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



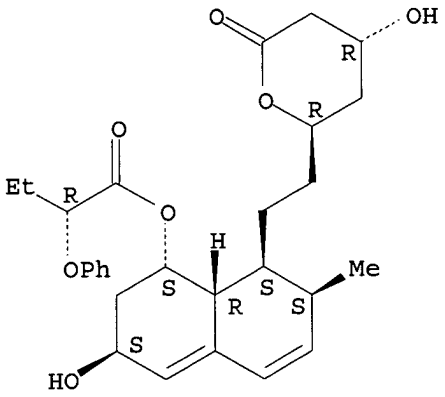
RN 161788-60-9 CAPLUS
CN Butanoic acid, 2-[(2-methyl-1-naphthalenyl)oxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



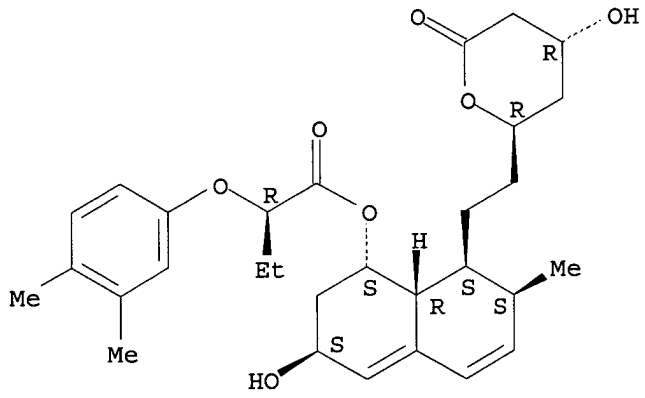
RN 161788-63-2 CAPLUS
CN Butanoic acid, 2-phenoxy-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



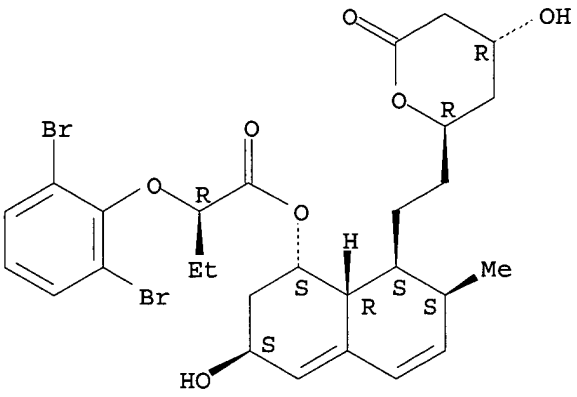
RN 161788-66-5 CAPLUS
CN Butanoic acid, 2-(3,4-dimethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



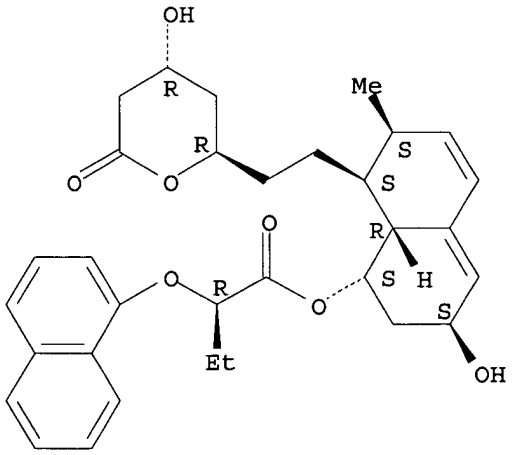
RN 161788-69-8 CAPLUS
CN Butanoic acid, 2-(2,6-dibromophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



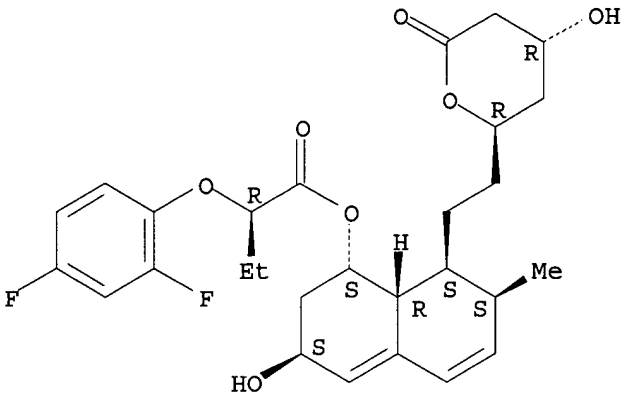
RN 161788-72-3 CAPLUS
CN Butanoic acid, 2-(1-naphthalenyloxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



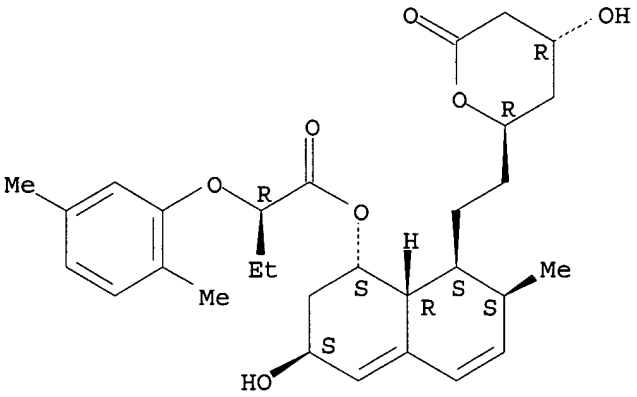
RN 161788-75-6 CAPLUS
CN Butanoic acid, 2-(2,4-difluorophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



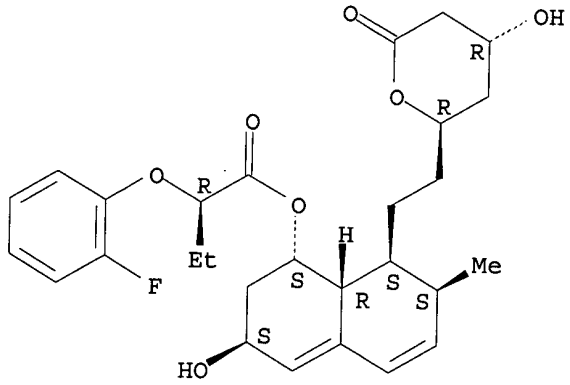
RN 161788-78-9 CAPLUS
CN Butanoic acid, 2-(2,5-dimethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



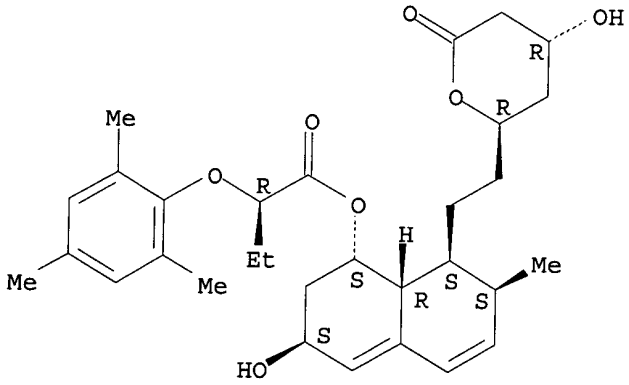
RN 161788-81-4 CAPLUS
CN Butanoic acid, 2-(2-fluorophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



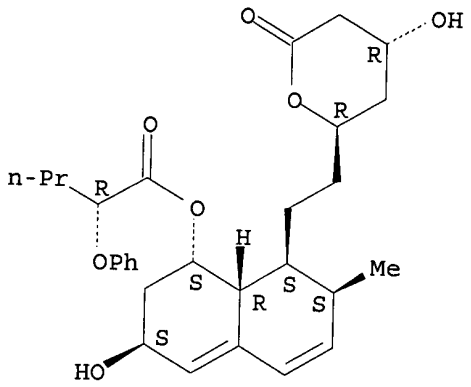
RN 161788-84-7 CAPLUS
CN Butanoic acid, 2-(2,4,6-trimethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



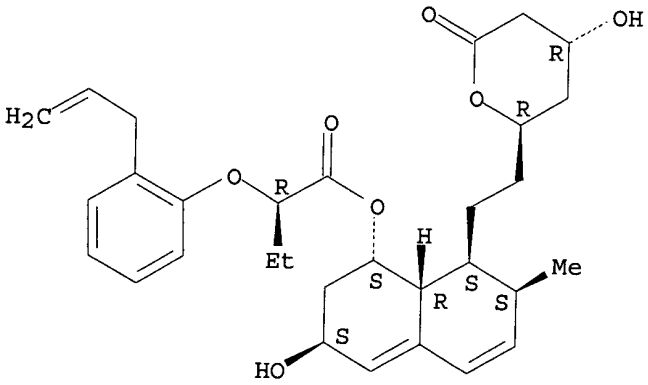
RN 161788-87-0 CAPLUS
CN Pentanoic acid, 2-phenoxy-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



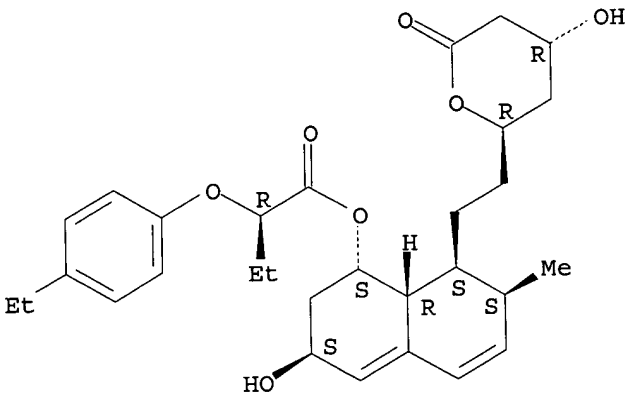
RN 161788-90-5 CAPLUS
CN Butanoic acid, 2-[2-(2-propenyl)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



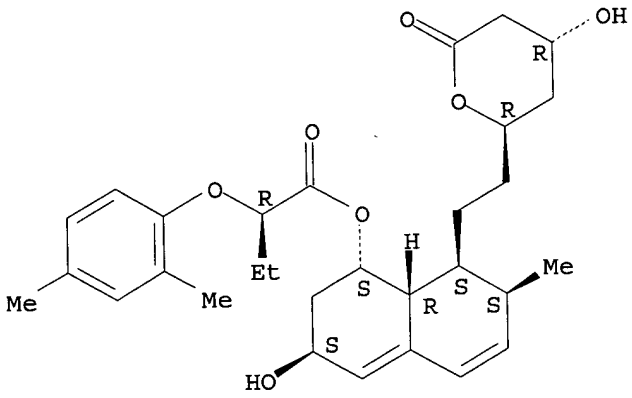
RN 161788-93-8 CAPLUS
CN Butanoic acid, 2-(4-ethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



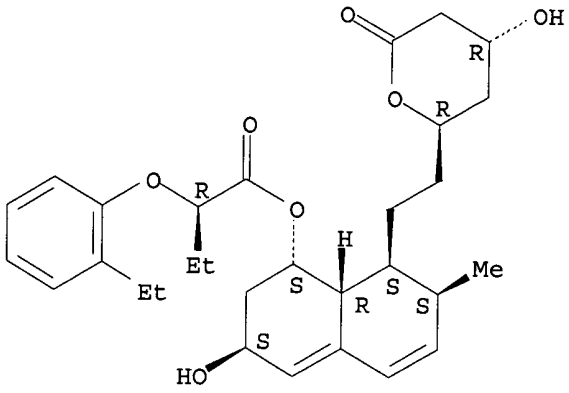
RN 161788-96-1 CAPLUS
CN Butanoic acid, 2-(2,4-dimethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



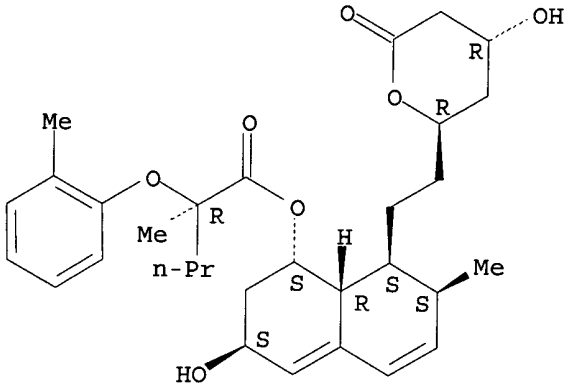
RN 161788-99-4 CAPLUS
CN Butanoic acid, 2-(2-ethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



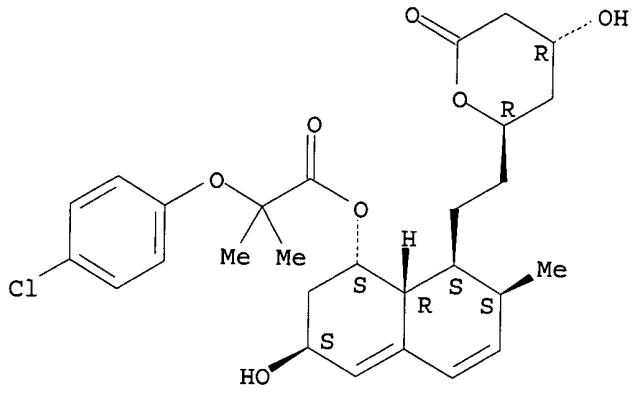
RN 161789-02-2 CAPLUS
CN Pentanoic acid, 2-methyl-2-(2-methylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



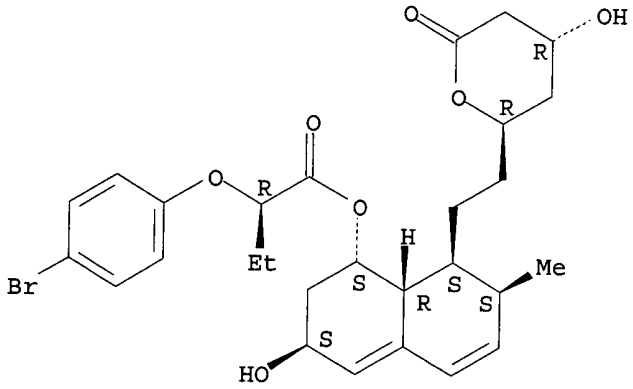
RN 161789-05-5 CAPLUS
CN Propanoic acid, 2-(4-chlorophenoxy)-2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



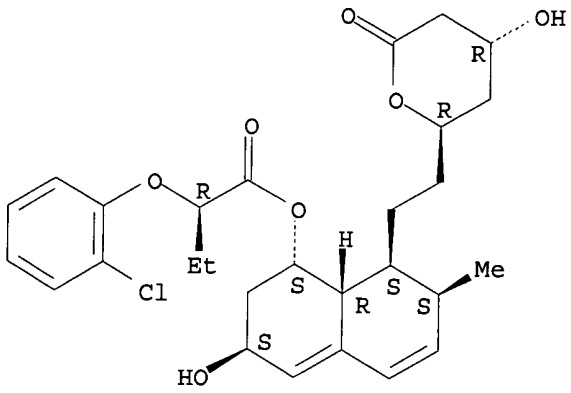
RN 161789-08-8 CAPLUS
CN Butanoic acid, 2-(4-bromophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



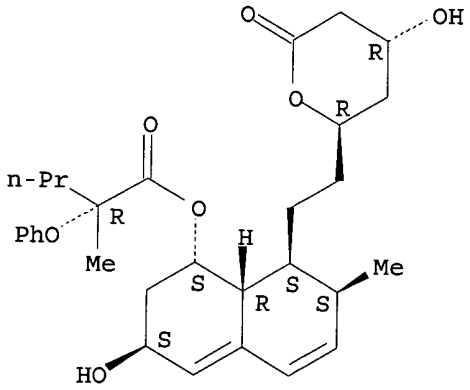
RN 161789-11-3 CAPLUS
CN Butanoic acid, 2-(2-chlorophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



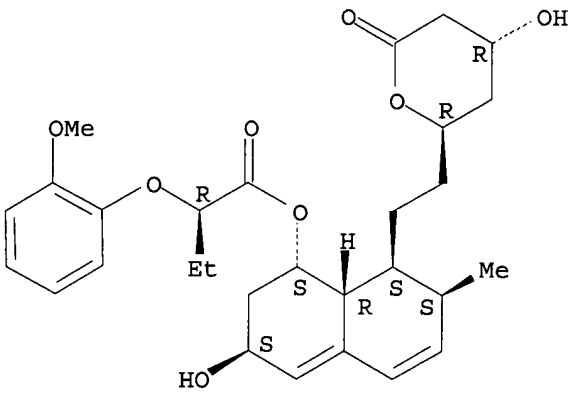
RN 161789-14-6 CAPLUS
CN Pentanoic acid, 2-methyl-2-phenoxy-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



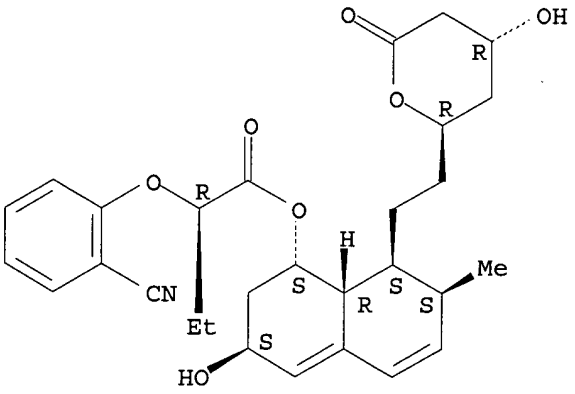
RN 161789-17-9 CAPLUS
CN Butanoic acid, 2-(2-methoxyphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



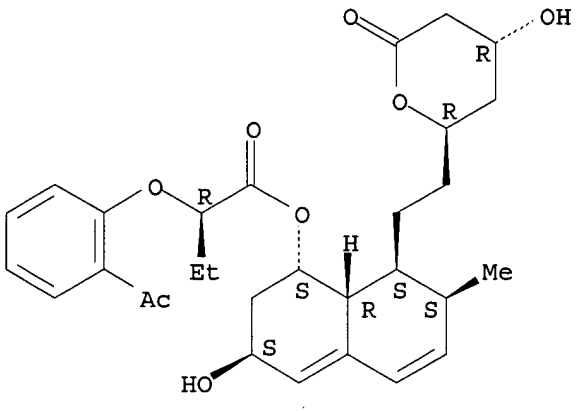
RN 161789-20-4 CAPLUS
CN Butanoic acid, 2-(2-cyanophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



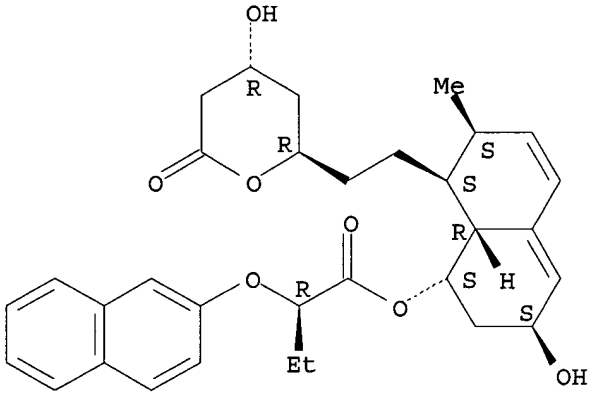
RN 161789-23-7 CAPLUS
CN Butanoic acid, 2-(2-acetylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



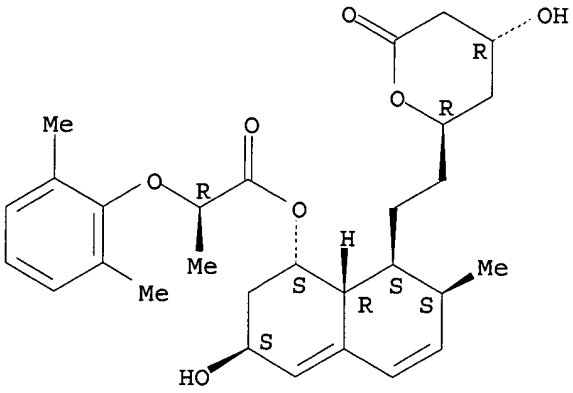
RN 161789-26-0 CAPLUS
CN Butanoic acid, 2-(2-naphthalenyloxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



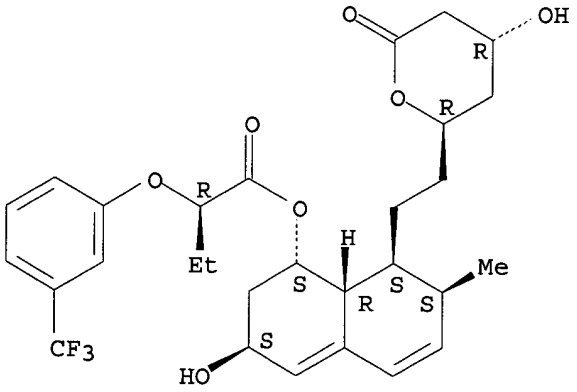
RN 161789-29-3 CAPLUS
CN Propanoic acid, 2-(2,6-dimethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



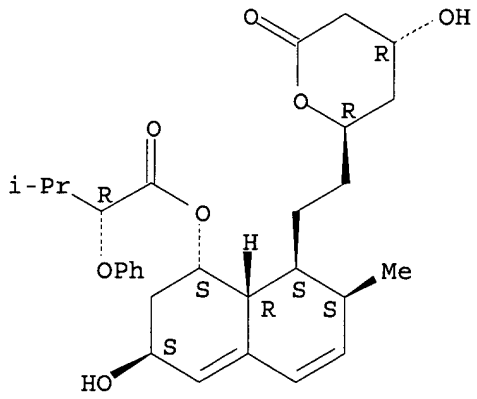
RN 161789-32-8 CAPLUS
CN Butanoic acid, 2-[3-(trifluoromethyl)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



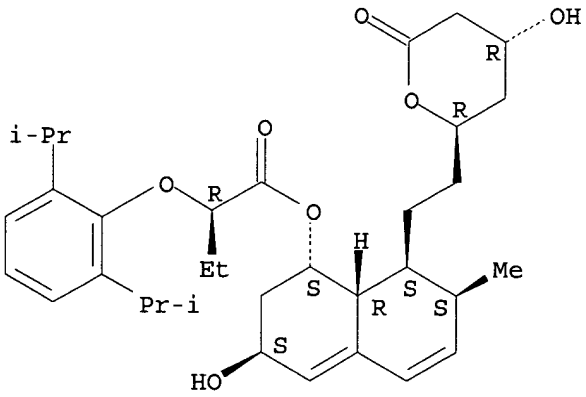
RN 161789-35-1 CAPLUS
CN Butanoic acid, 3-methyl-2-phenoxy-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



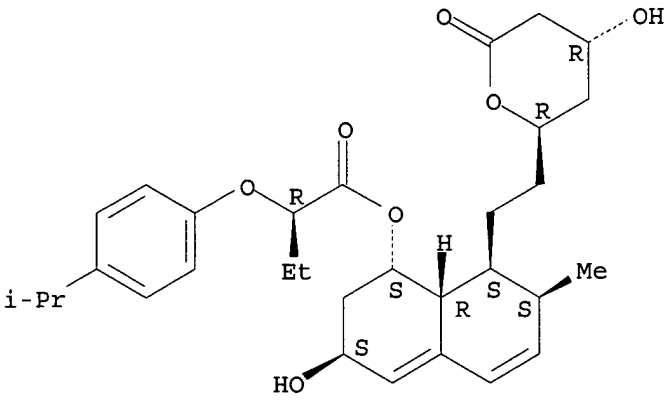
RN 161789-38-4 CAPLUS
CN Butanoic acid, 2-[2,6-bis(1-methylethyl)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



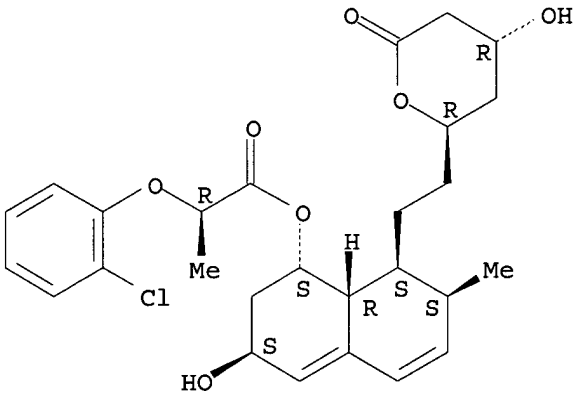
RN 161789-41-9 CAPLUS
CN Butanoic acid, 2-[4-(1-methylethyl)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



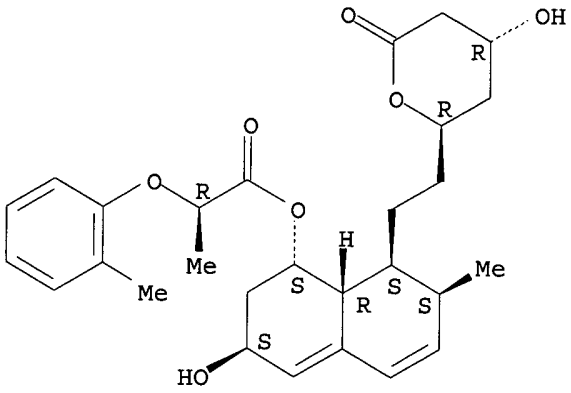
RN 161789-44-2 CAPLUS
CN Propanoic acid, 2-(2-chlorophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



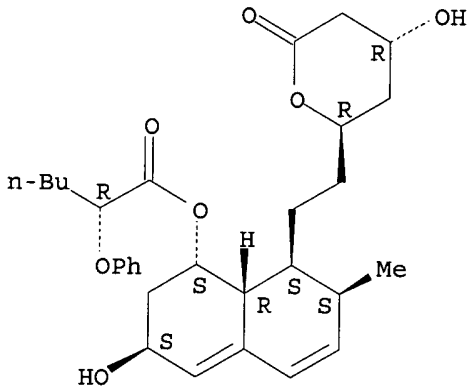
RN 161789-47-5 CAPLUS
CN Propanoic acid, 2-(2-methylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



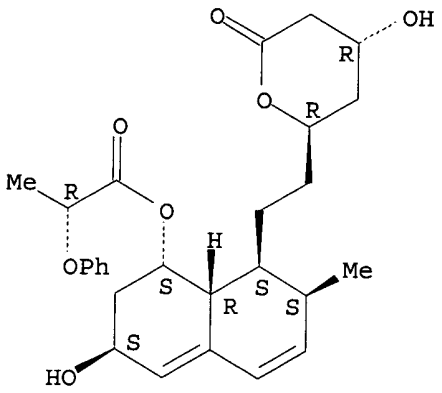
RN 161789-50-0 CAPLUS
CN Hexanoic acid, 2-phenoxy-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



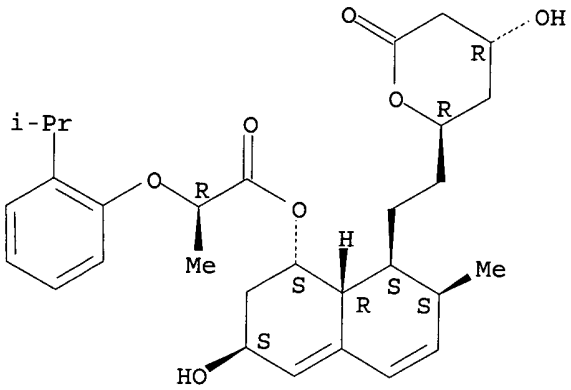
RN 161789-53-3 CAPLUS
CN Propanoic acid, 2-phenoxy-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



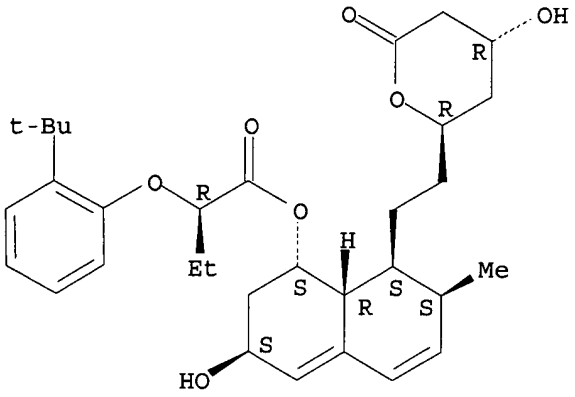
RN 161789-56-6 CAPLUS
CN Propanoic acid, 2-[2-(1-methylethyl)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



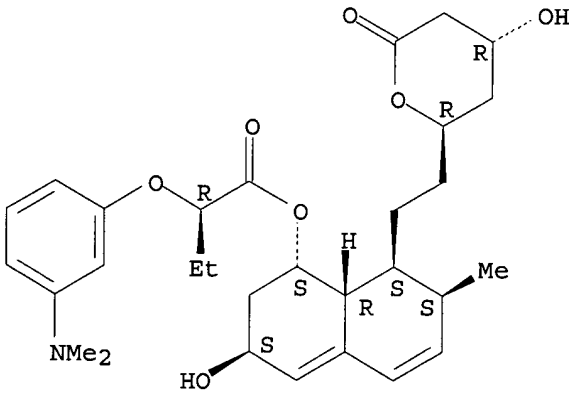
RN 161789-59-9 CAPLUS
CN Butanoic acid, 2-[2-(1,1-dimethylethyl)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



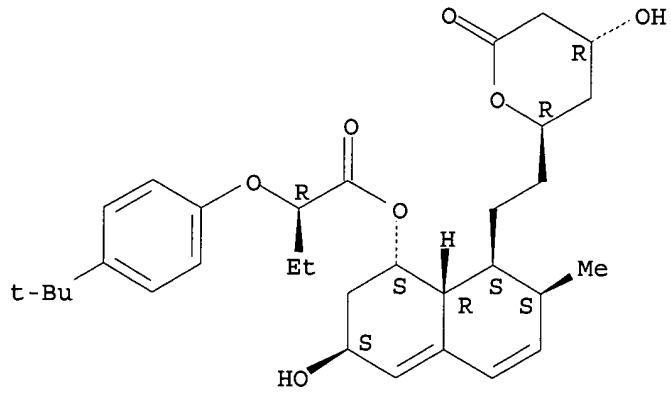
RN 161789-62-4 CAPLUS
CN Butanoic acid, 2-[3-(dimethylamino)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



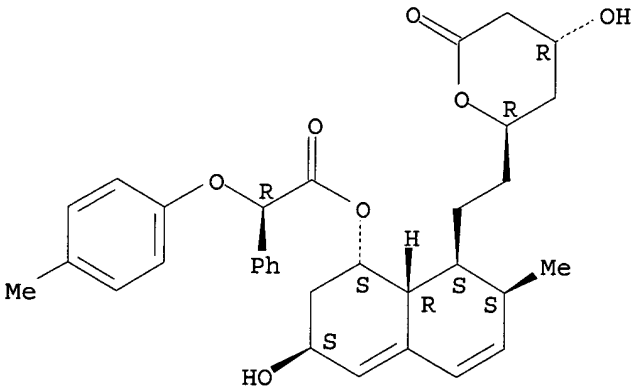
RN 161789-65-7 CAPLUS
CN Butanoic acid, 2-[4-(1,1-dimethylethyl)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



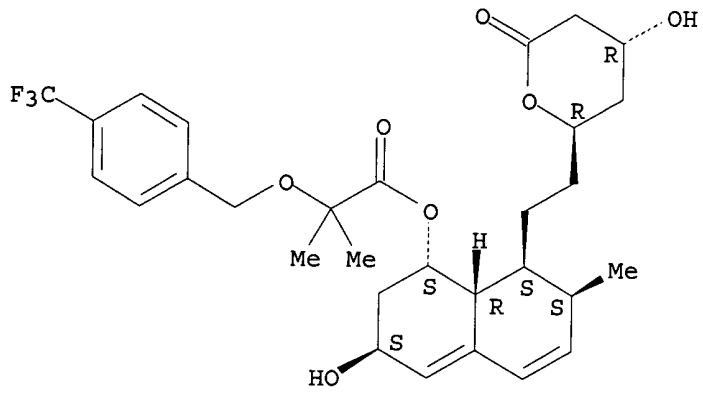
RN 161789-68-0 CAPLUS
CN Benzeneacetic acid, .alpha.-(4-methylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



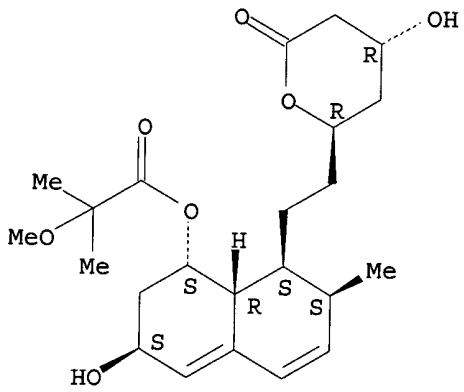
RN 161789-71-5 CAPLUS
CN Propanoic acid, 2-methyl-2-[[4-(trifluoromethyl)phenyl]methoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



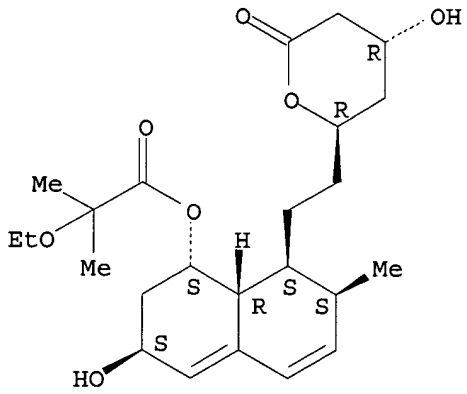
RN 161789-74-8 CAPLUS
CN Propanoic acid, 2-methoxy-2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



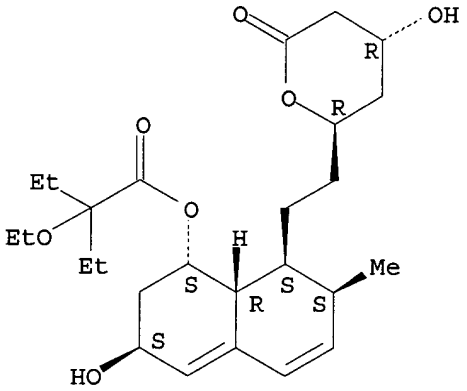
RN 161789-77-1 CAPLUS
CN Propanoic acid, 2-ethoxy-2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



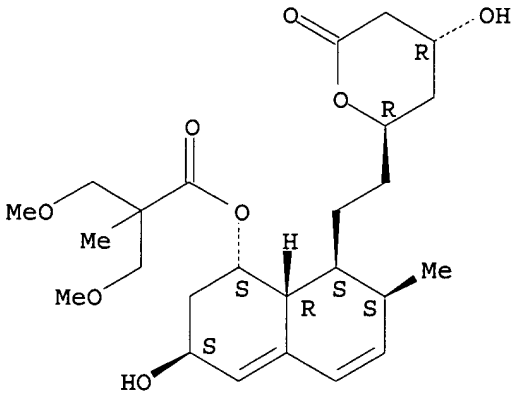
RN 161789-82-8 CAPLUS
CN Butanoic acid, 2-ethoxy-2-ethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



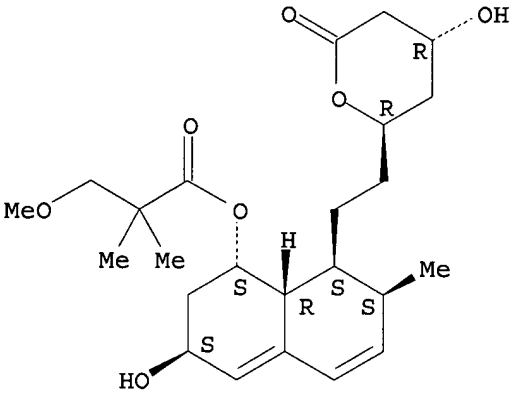
RN 161789-85-1 CAPLUS
CN Propanoic acid, 3-methoxy-2-(methoxymethyl)-2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



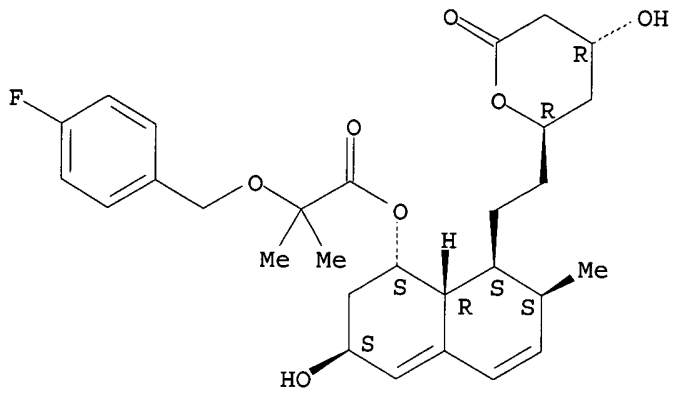
RN 161789-88-4 CAPLUS
CN Propanoic acid, 3-methoxy-2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



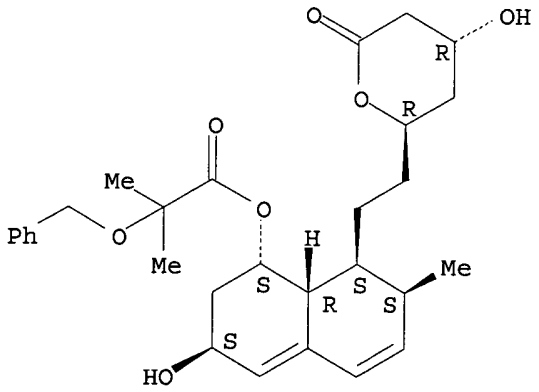
RN 161789-91-9 CAPLUS
CN Propanoic acid, 2-[(4-fluorophenyl)methoxy]-2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



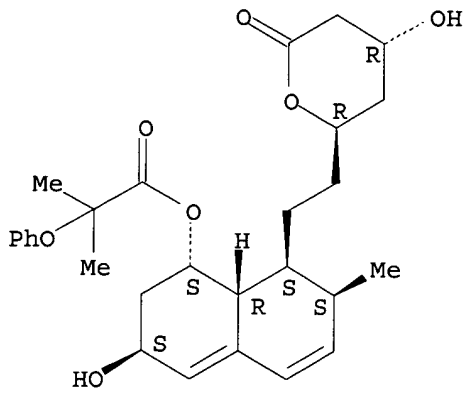
RN 161789-94-2 CAPLUS
CN Propanoic acid, 2-methyl-2-(phenylmethoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



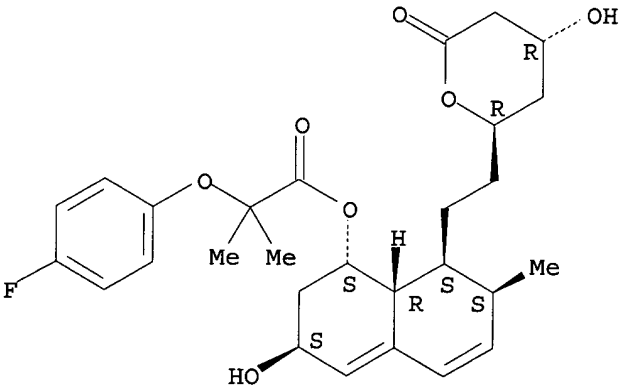
RN 161789-97-5 CAPLUS
CN Propanoic acid, 2-methyl-2-phenoxy-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



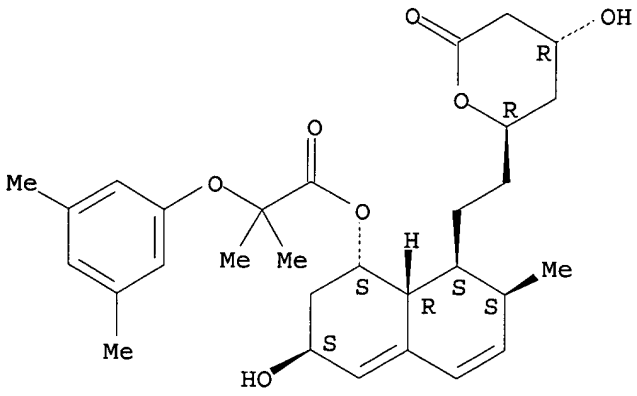
RN 161790-00-7 CAPLUS
CN Propanoic acid, 2-(4-fluorophenoxy)-2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



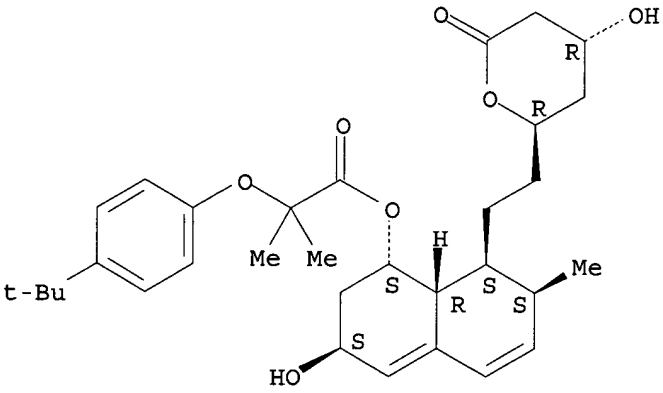
RN 161790-03-0 CAPLUS
CN Propanoic acid, 2-(3,5-dimethylphenoxy)-2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



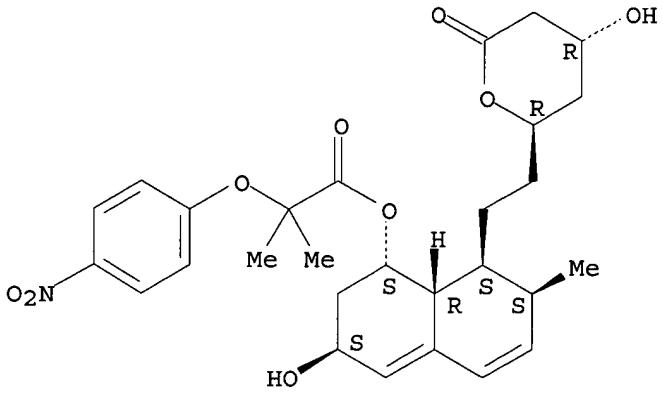
RN 161790-06-3 CAPLUS
CN Propanoic acid, 2-[4-(1,1-dimethylethyl)phenoxy]-2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



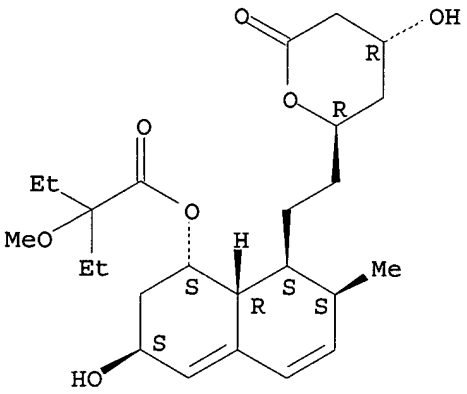
RN 161790-09-6 CAPLUS
CN Propanoic acid, 2-methyl-2-(4-nitrophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



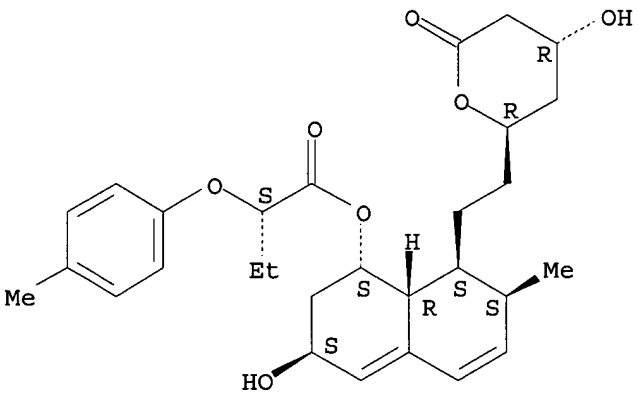
RN 161790-52-9 CAPLUS
CN Butanoic acid, 2-ethyl-2-methoxy-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



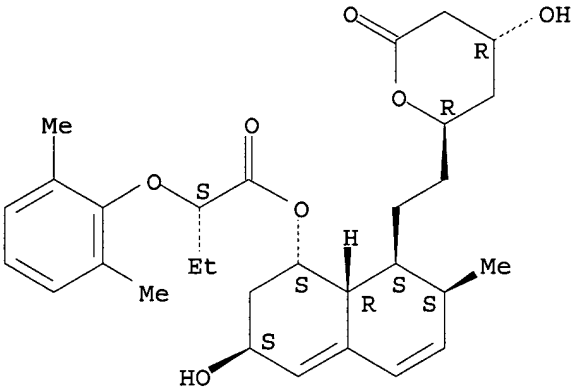
RN 161903-18-0 CAPLUS
CN Butanoic acid, 2-(4-methylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



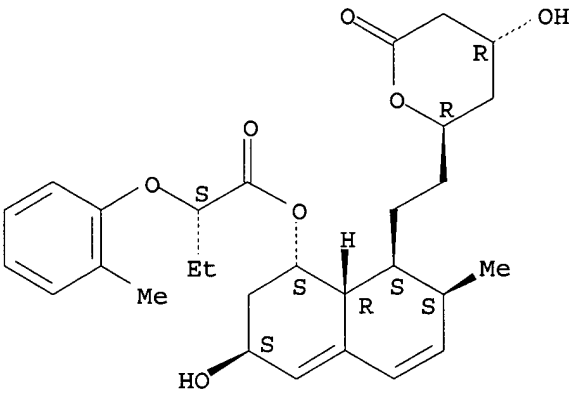
RN 161903-22-6 CAPLUS
CN Butanoic acid, 2-(2,6-dimethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



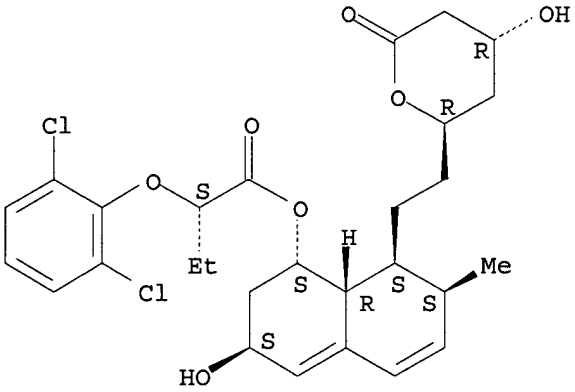
RN 161903-28-2 CAPLUS
CN Butanoic acid, 2-(2-methylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



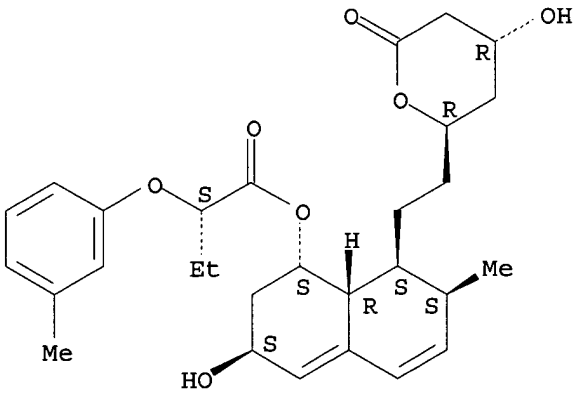
RN 161903-31-7 CAPLUS
CN Butanoic acid, 2-(2,6-dichlorophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



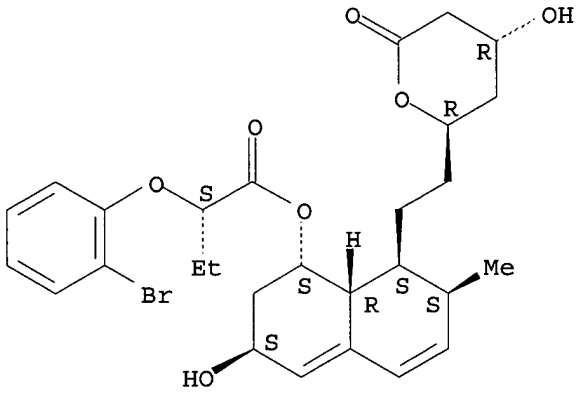
RN 161903-34-0 CAPLUS
CN Butanoic acid, 2-(3-methylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



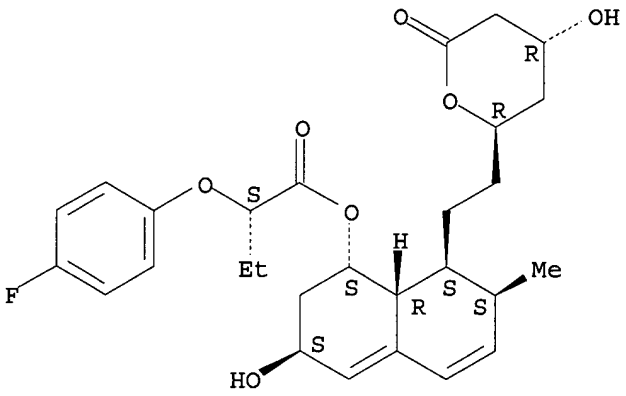
RN 161903-37-3 CAPLUS
CN Butanoic acid, 2-(2-bromophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



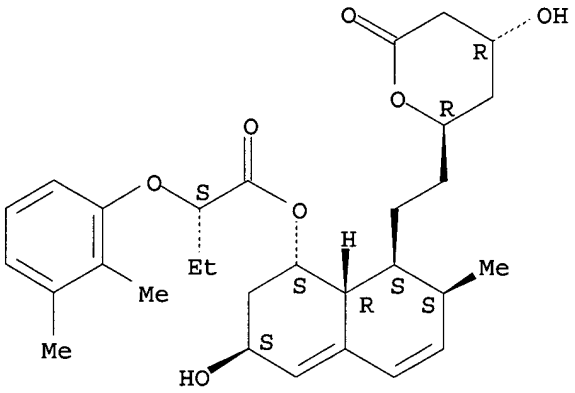
RN 161903-40-8 CAPLUS
CN Butanoic acid, 2-(4-fluorophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



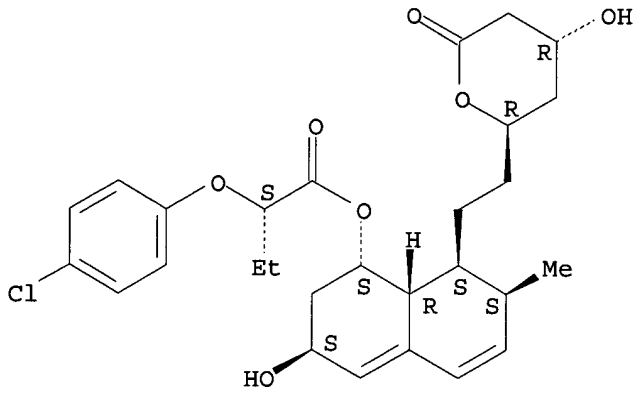
RN 161903-43-1 CAPLUS
CN Butanoic acid, 2-(2,3-dimethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



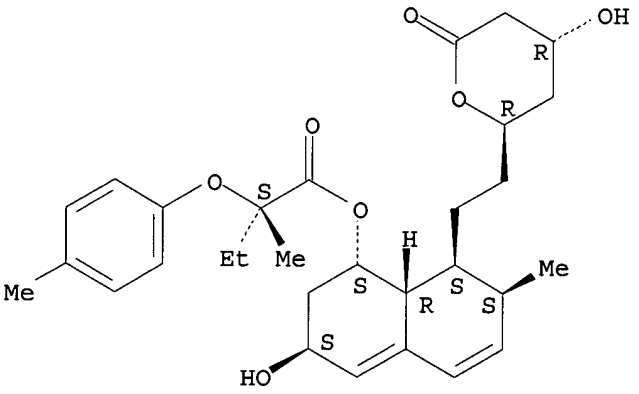
RN 161903-46-4 CAPLUS
CN Butanoic acid, 2-(4-chlorophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



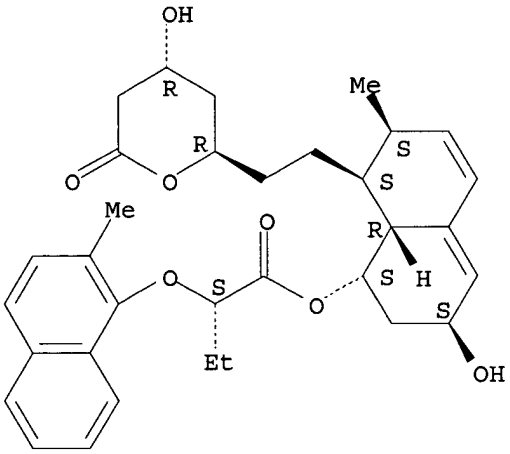
RN 161903-49-7 CAPLUS
CN Butanoic acid, 2-methyl-2-(4-methylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



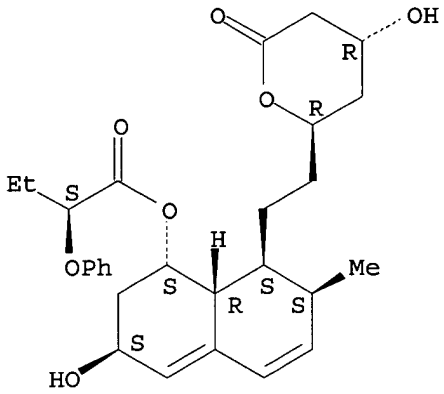
RN 161903-52-2 CAPLUS
CN Butanoic acid, 2-[(2-methyl-1-naphthalenyl)oxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



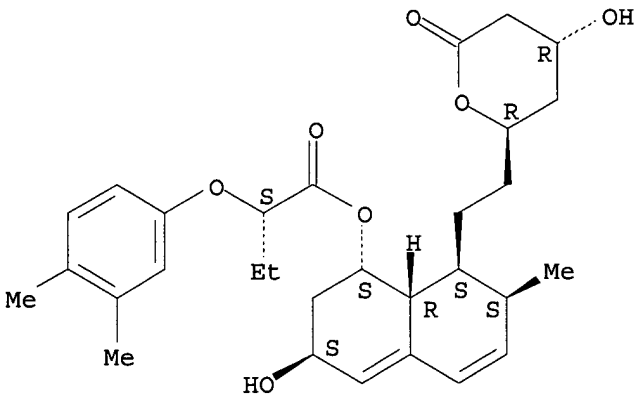
RN 161903-55-5 CAPLUS
CN Butanoic acid, 2-phenoxy-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



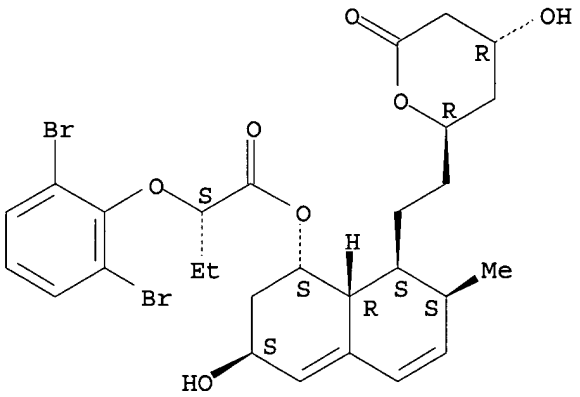
RN 161903-58-8 CAPLUS
CN Butanoic acid, 2-(3,4-dimethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



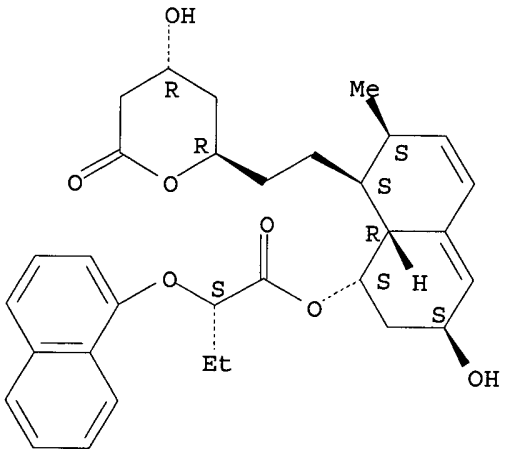
RN 161903-61-3 CAPLUS
CN Butanoic acid, 2-(2,6-dibromophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



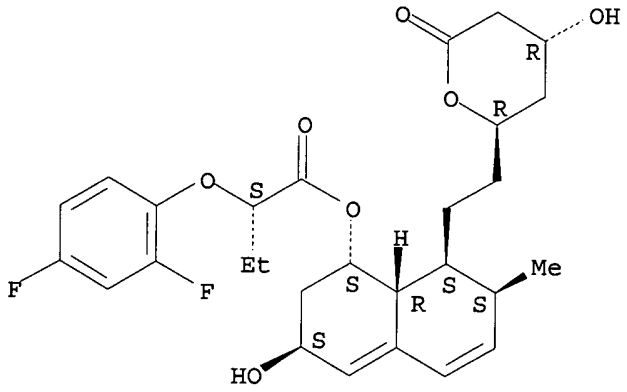
RN 161903-64-6 CAPLUS
CN Butanoic acid, 2-(1-naphthalenyloxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



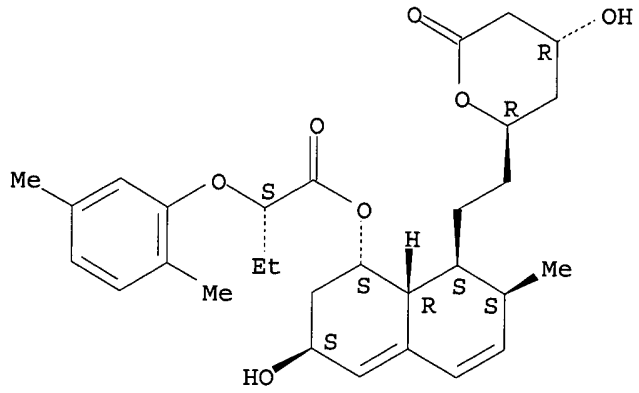
RN 161903-67-9 CAPLUS
CN Butanoic acid, 2-(2,4-difluorophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



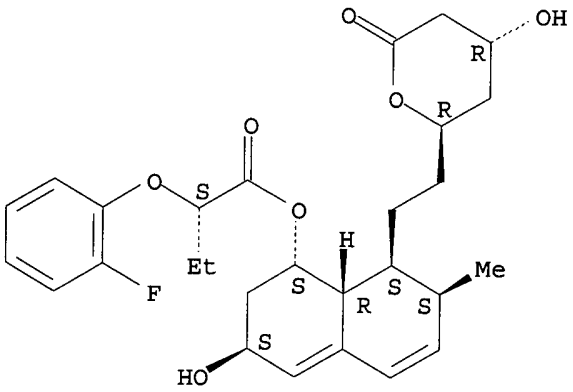
RN 161903-70-4 CAPLUS
CN Butanoic acid, 2-(2,5-dimethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



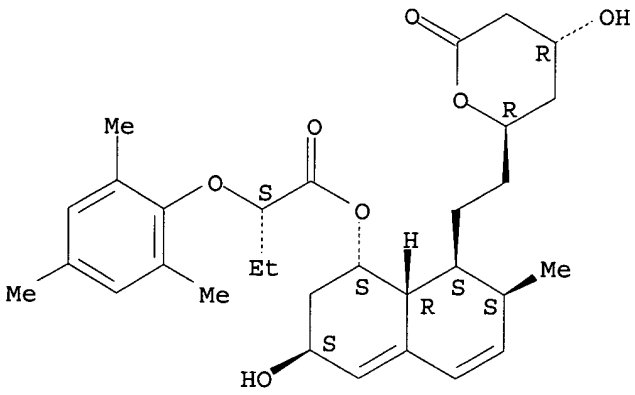
RN 161903-73-7 CAPLUS
CN Butanoic acid, 2-(2-fluorophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



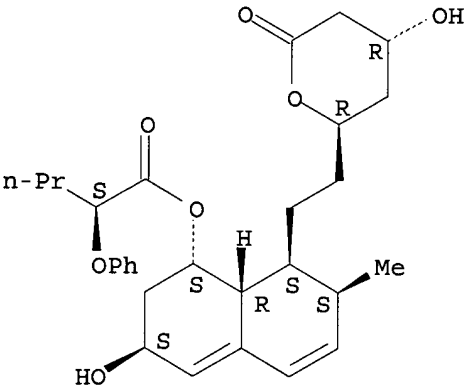
RN 161903-76-0 CAPLUS
CN Butanoic acid, 2-(2,4,6-trimethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



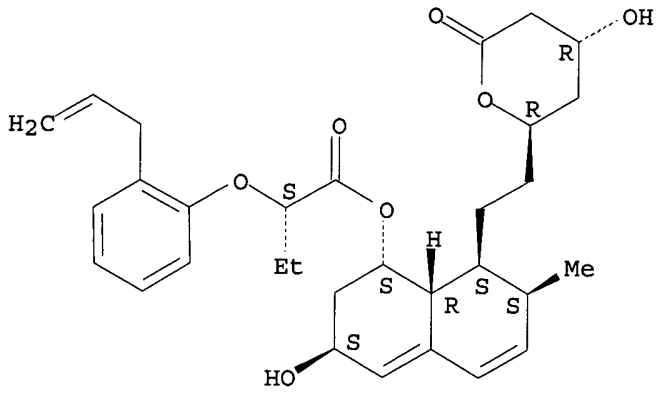
RN 161903-79-3 CAPLUS
CN Pentanoic acid, 2-phenoxy-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



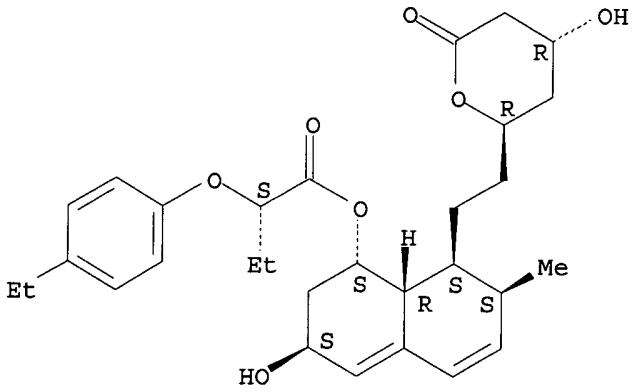
RN 161903-82-8 CAPLUS
CN Butanoic acid, 2-[2-(2-propenyl)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



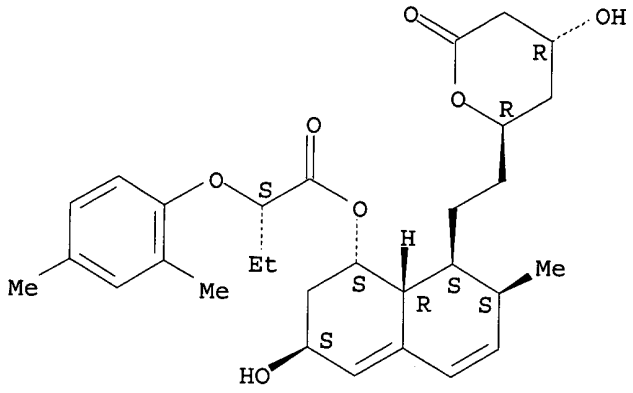
RN 161903-85-1 CAPLUS
CN Butanoic acid, 2-(4-ethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



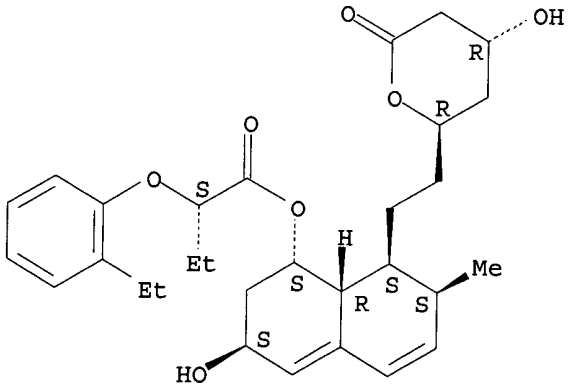
RN 161903-88-4 CAPLUS
CN Butanoic acid, 2-(2,4-dimethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



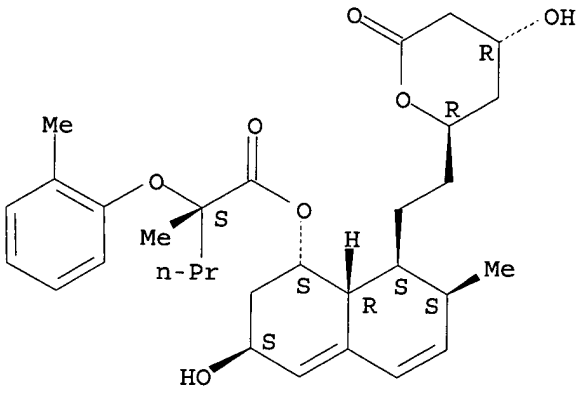
RN 161903-91-9 CAPLUS
CN Butanoic acid, 2-(2-ethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



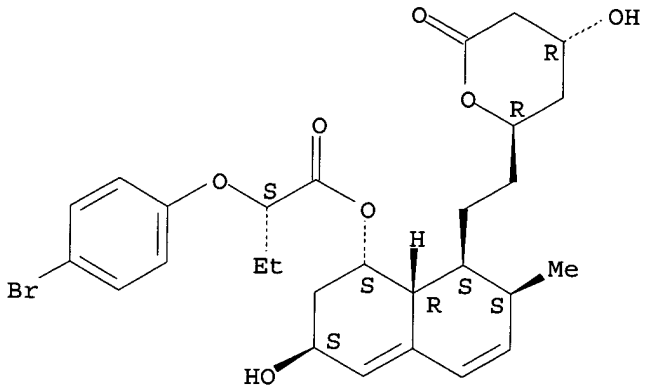
RN 161903-94-2 CAPLUS
CN Pentanoic acid, 2-methyl-2-(2-methylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



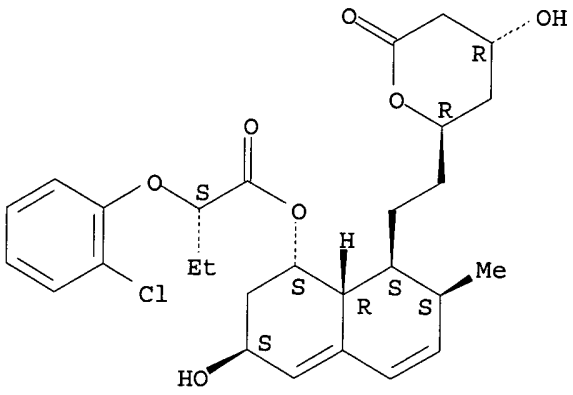
RN 161903-97-5 CAPLUS
CN Butanoic acid, 2-(4-bromophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



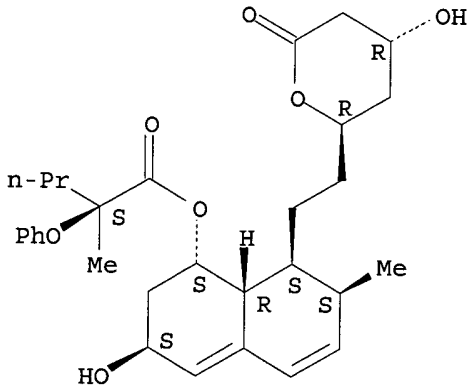
RN 161904-00-3 CAPLUS
CN Butanoic acid, 2-(2-chlorophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



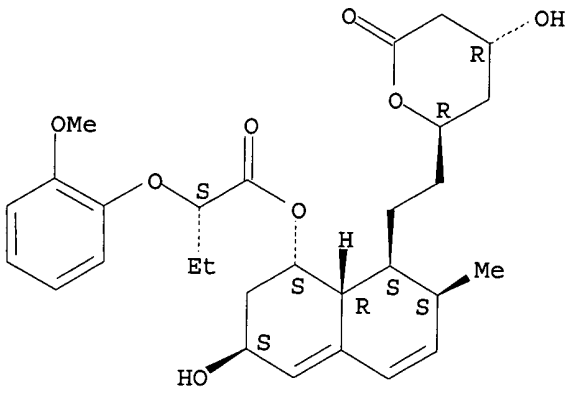
RN 161904-03-6 CAPLUS
CN Pentanoic acid, 2-methyl-2-phenoxy-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



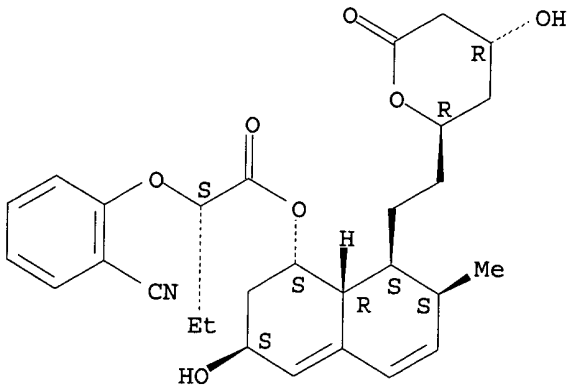
RN 161904-06-9 CAPLUS
CN Butanoic acid, 2-(2-methoxyphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



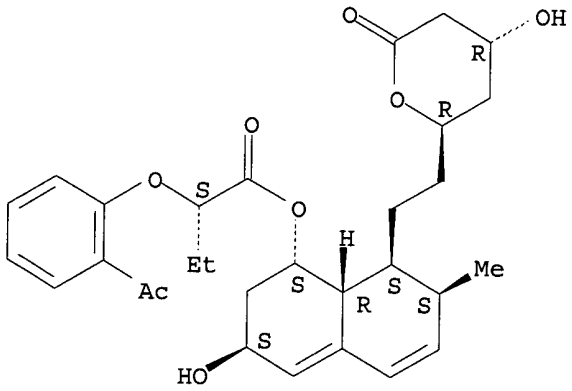
RN 161904-09-2 CAPLUS
CN Butanoic acid, 2-(2-cyanophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



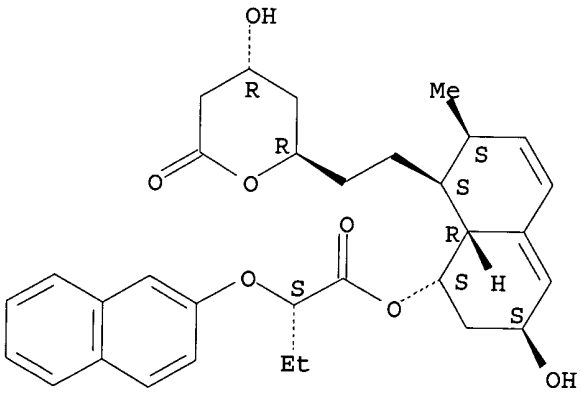
RN 161904-12-7 CAPLUS
CN Butanoic acid, 2-(2-acetylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



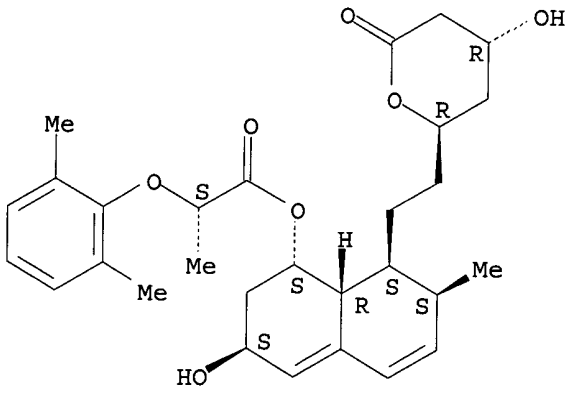
RN 161904-15-0 CAPLUS
CN Butanoic acid, 2-(2-naphthalenyloxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



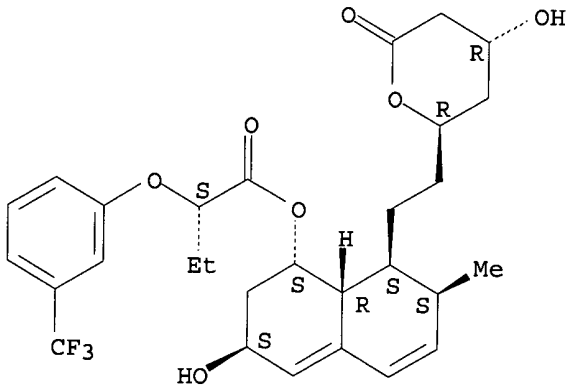
RN 161904-18-3 CAPLUS
CN Propanoic acid, 2-(2,6-dimethylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



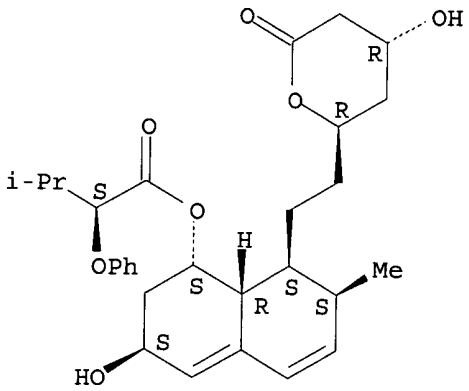
RN 161904-21-8 CAPLUS
CN Butanoic acid, 2-[3-(trifluoromethyl)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



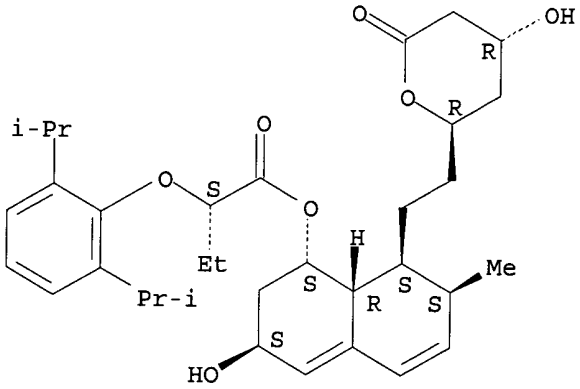
RN 161904-24-1 CAPLUS
CN Butanoic acid, 3-methyl-2-phenoxy-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



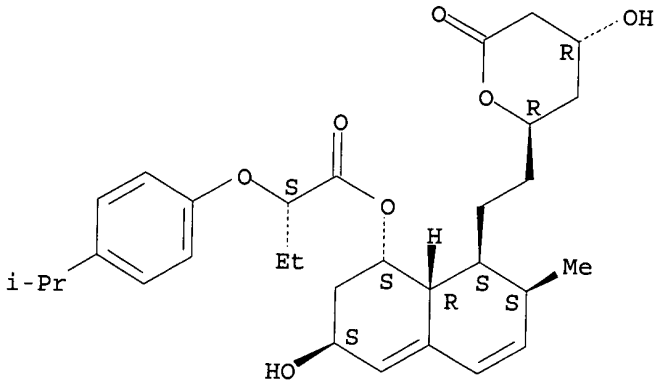
RN 161904-27-4 CAPLUS
CN Butanoic acid, 2-[2,6-bis(1-methylethyl)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



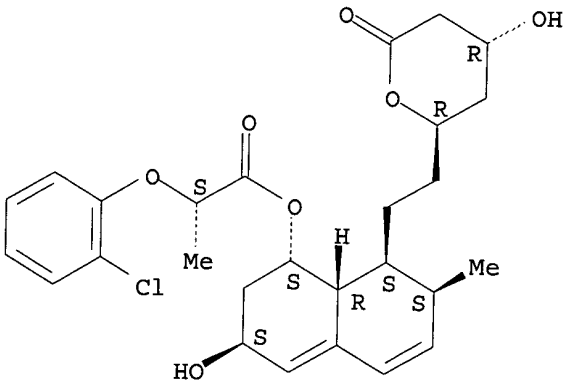
RN 161904-30-9 CAPLUS
CN Butanoic acid, 2-[4-(1-methylethyl)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



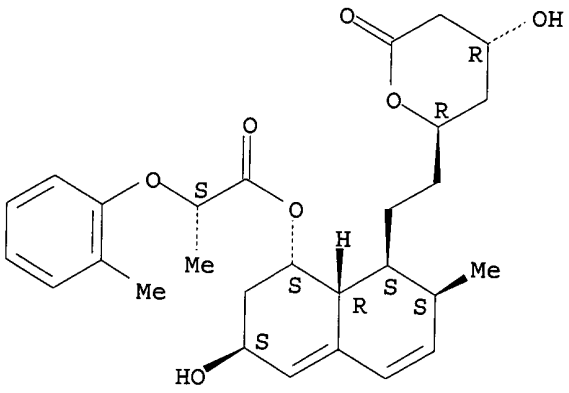
RN 161904-33-2 CAPLUS
CN Propanoic acid, 2-(2-chlorophenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



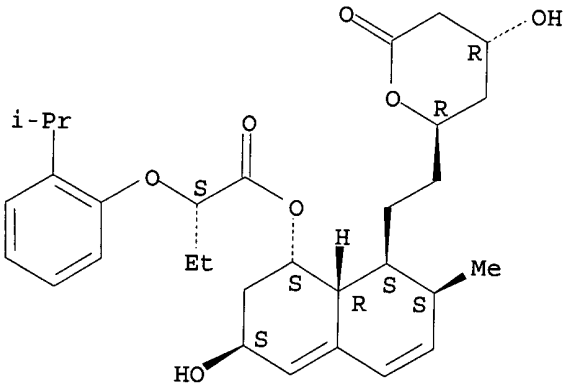
RN 161904-36-5 CAPLUS
CN Propanoic acid, 2-(2-methylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



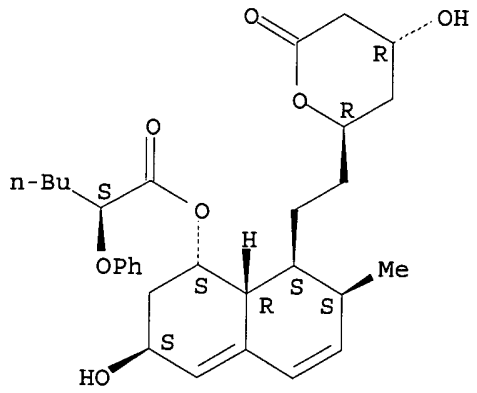
RN 161904-38-7 CAPLUS
CN Butanoic acid, 2-[2-(1-methylethyl)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



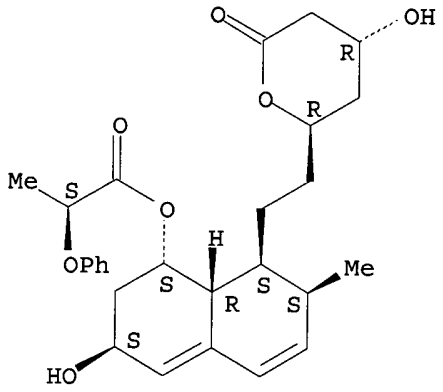
RN 161904-40-1 CAPLUS
CN Hexanoic acid, 2-phenoxy-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



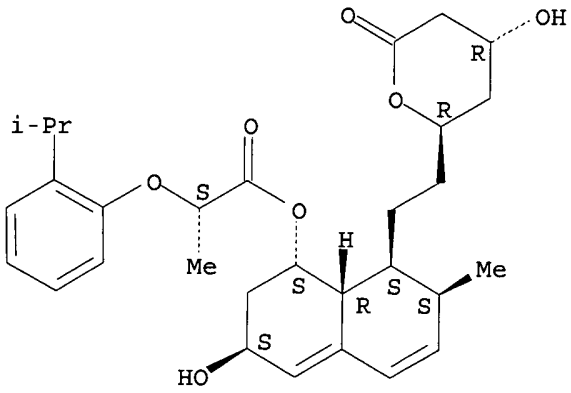
RN 161904-43-4 CAPLUS
CN Propanoic acid, 2-phenoxy-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



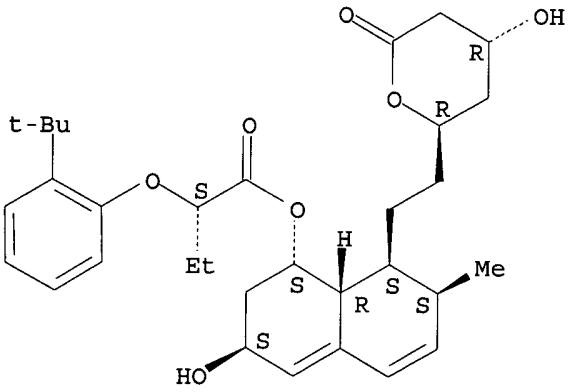
RN 161904-46-7 CAPLUS
CN Propanoic acid, 2-[2-(1-methylethyl)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



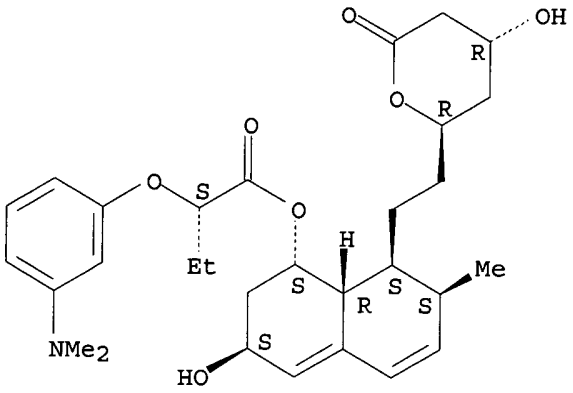
RN 161904-49-0 CAPLUS
CN Butanoic acid, 2-[2-(1,1-dimethylethyl)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



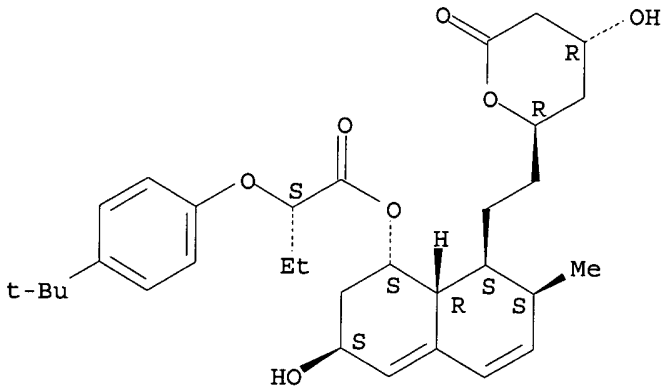
RN 161904-52-5 CAPLUS
CN Butanoic acid, 2-[3-(dimethylamino)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



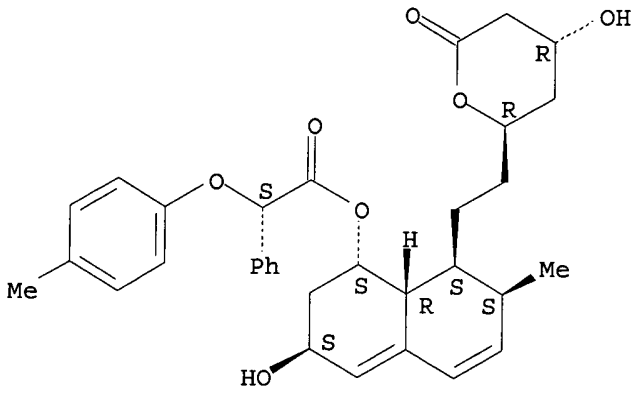
RN 161904-55-8 CAPLUS
CN Butanoic acid, 2-[4-(1,1-dimethylethyl)phenoxy]-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



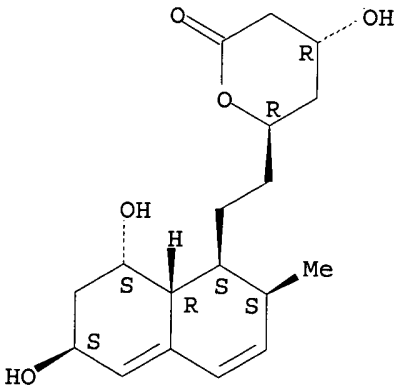
RN 161904-58-1 CAPLUS
CN Benzeneacetic acid, .alpha.-(4-methylphenoxy)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **159345-93-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of hexahydronaphthalene ester derivs. as anticholesteremics)
RN 159345-93-4 CAPLUS
CN 2H-Pyran-2-one, 6-[2-(1,2,6,7,8,8a-hexahydro-6,8-dihydroxy-2-methyl-1-naphthalenyl)ethyl]tetrahydro-4-hydroxy-, [1S-[1.alpha.(2S*,4S*),2.alpha.,6.alpha.,8.beta.,8a.alpha.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 30 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:316101 CAPLUS
DOCUMENT NUMBER: 122:263678
TITLE: Synthesis of hydroxymethylglutaryl-CoA reductase inhibitors
INVENTOR(S): Carta, Giorgio; Conder, Michael J.; Gainer, John Lloyd; Stieberg, Robert W.; Vinci, Victor A.; Weber, Timothy Wallace
PATENT ASSIGNEE(S): Merck and Co., Inc., USA; University of Virginia Alumni Patents Foundation
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

Golam Shameem

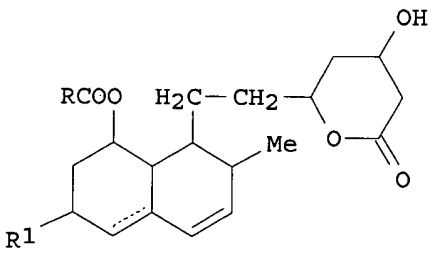
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9426920	A1	19941124	WO 1994-US5019	19940506
W: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TT, UA, US, UZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5420024	A	19950530	US 1993-60847	19930511
CA 2161788	AA	19941124	CA 1994-2161788	19940506
AU 9469072	A1	19941212	AU 1994-69072	19940506
AU 673268	B2	19961031		
EP 698111	A1	19960228	EP 1994-917312	19940506
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 08510128	T2	19961029	JP 1994-525564	19940506

PRIORITY APPLN. INFO.: US 1993-60847 19930511
WO 1994-US5019 19940506

OTHER SOURCE(S): MARPAT 122:263678

GI



I R = alkyl; R^1 = H, alkyl

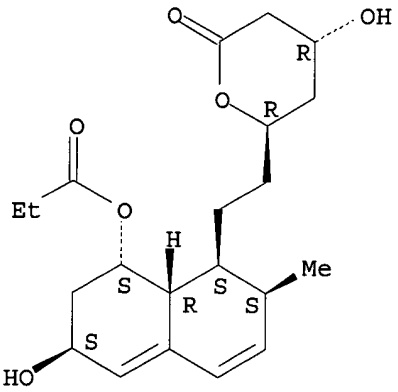
AB HMG-CoA reductase inhibitors of formula (I) are formed by esterification employing an immobilized lipase in a nonaq. org. solvent. Thus, lovastatin diol lactone was incubated with nylon-immobilized lipase type VII from Candida cylindracea and 2-methylbutyric acid in a solvent of 1:1 CHCl3-hexane and shaken at room temp. Lovastatin formation occurred at a rate of 3.2 .times. 10-5 mol/h-g lipase.

IT **160522-02-1P**
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis of hydroxymethylglutaryl-CoA reductase inhibitors with lipase)

RN 160522-02-1 CAPLUS

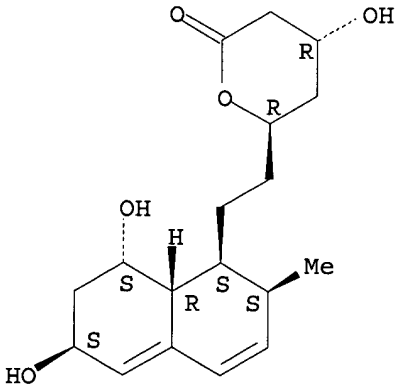
CN 2H-Pyran-2-one, 6-[2-[1,2,6,7,8,8a-hexahydro-6-hydroxy-2-methyl-8-(1-oxopropoxy)-1-naphthalenyl]ethyl]tetrahydro-4-hydroxy-, [1S-[1.alpha.(4S*,6S*),2.alpha.,6.alpha.,8.beta.,8a.alpha.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **159345-93-4**, Pravastatin diol lactone
RL: BPR (Biological process); RCT (Reactant); BIOL (Biological study); PROC (Process)
(synthesis of hydroxymethylglutaryl-CoA reductase inhibitors with lipase)
RN 159345-93-4 CAPLUS
CN 2H-Pyran-2-one, 6-[2-(1,2,6,7,8,8a-hexahydro-6,8-dihydroxy-2-methyl-1-naphthalenyl)ethyl]tetrahydro-4-hydroxy-, [1S-[1.alpha.(2S*,4S*),2.alpha.,6.alpha.,8.beta.,8a.alpha.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 31 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:80747 CAPLUS
DOCUMENT NUMBER: 122:167
TITLE: Studies on drug metabolism using liquid chromatography/mass spectrometry: comparison of three liquid chromatographic/mass spectrometric interfaces
AUTHOR(S): Iwabuchi, Haruo; Kitazawa, Eiichi; Kobayashi, Nobuhiro; Watanabe, Hidetoshi; Kanai, Michiko; Nakamura, Kan-ichi
CORPORATE SOURCE: Analytical Metabolic Res. Laboratories, Sankyo Co. Ltd., Tokyo, 140, Japan
SOURCE: Biol. Mass Spectrom. (1994), 23(9), 540-6
CODEN: BIMSEH; ISSN: 1052-9306

Golam Shameem

DOCUMENT TYPE: Journal
LANGUAGE: English

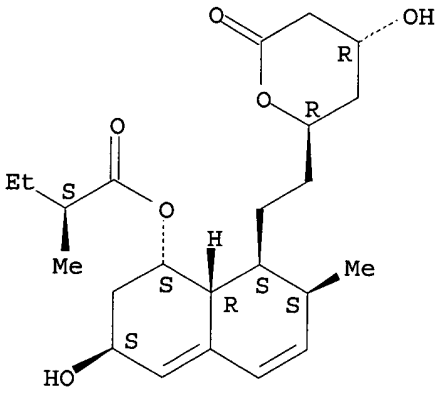
AB Three ionization methods of liq. chromatog./mass spectrometry (LC/MS) [atm. pressure chem. ionization (APCI), thermospray (TSP) and electrospray ionization (ESI)], were characterized by investigating the relationships between sensitivities and polarities of compds., Log P values and mass spectrometry of three hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors-pravastatin sodium (including its metabolites and related compds.), lovastatin and simvastatin-were measured. Their log P values ranged from -2.49 to 4.40, and in LC/MS each of the ionization methods gave different quasi-mol. ions and sensitivities. The APCI method showed a high sensitivity of several nanograms for hydrophobic compds. (log P > 2), but was not effective for hydrophilic compds., such as glutathione conjugate. The TSP method was applicable to all compds. used in this study, and was more sensitive for hydrophobic compds. The ESI method was also applicable to all compds. (.ltoreq.20 ng), and was 10-100 times more sensitive than the other methods in the case of hydrophilic compds. These results suggest that hydrophobicity of compds. related to efficiency of LC/MS ionization.

IT **85956-22-5**, R 414
RL: ANT (Analyte); ANST (Analytical study)
(detn. of drug metab. using liq. chromatog. mass spectrometry and comparison of three liq. chromatog. mass spectrometric interfaces)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 32 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:26212 CAPLUS
DOCUMENT NUMBER: 122:239339
TITLE: Preparation of hexahydronaphthyl ester anticholesteremics
INVENTOR(S): Kogen, Hiroshi; Tishihara, Sadao; Koga, Teiichiro; Kitazawa, Eiichi; Serizawa, Nobufusa; Hamano, Kiyoshi
PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 154 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

Golam Shameem

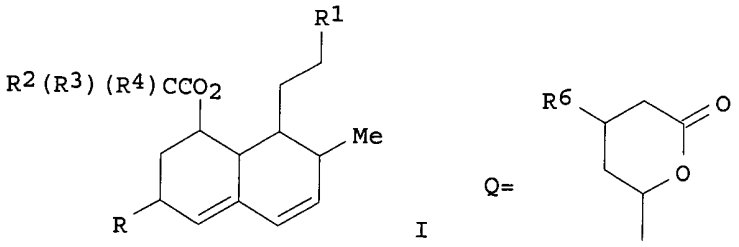
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 605230	A1	19940706	EP 1993-310536	19931224
EP 605230	B1	19970827		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CA 2112442	AA	19940629	CA 1993-2112442	19931224
AU 9352699	A1	19940707	AU 1993-52699	19931224
AU 670468	B2	19960718		
AT 157346	E	19970915	AT 1993-310536	19931224
ES 2108238	T3	19971216	ES 1993-310536	19931224
NO 9304852	A	19940629	NO 1993-4852	19931227
HU 65593	A2	19940728	HU 1993-3762	19931227
CZ 280492	B6	19960117	CZ 1993-2900	19931227
RU 2104997	C1	19980220	RU 1993-56837	19931227
IL 108194	A1	19980222	IL 1993-108194	19931227
ZA 9309741	A	19940815	ZA 1993-9741	19931228
JP 06247894	A2	19940906	JP 1993-335405	19931228
FI 9305895	A	19941019	FI 1993-5895	19931228
CN 1094707	A	19941109	CN 1993-121768	19931228
CN 1039642	B	19980902		
US 5451688	A	19950919	US 1993-174661	19931228
US 5827855	A	19981027	US 1995-579840	19951228

PRIORITY APPLN. INFO.: JP 1992-349034 A 19921228
US 1993-174661 A3 19931228
US 1995-435725 B3 19950505

OTHER SOURCE(S): MARPAT 122:239339

GI



AB The title compds. [I; R = H, OR6; R6 = H, hydroxy-protecting groups, C1-6 alkyl, (un)substituted C1-6 alkenesulfonyl, (un)substituted arylsulfonyl, etc.; R1 = Q, CH(OR6)CH2CH(OR6)CH2CO2R5; R5 = H, carboxy-protecting group; R2 = C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl; R3,R4 = H, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl; when R2 = Et and R3 = H then R4 .noteq. Me, when R2 = Et and R3 = alkyl then R4 .noteq. alkyl], useful for lowering blood cholesterol levels and inhibiting HMG-CoA reductase activity, are prepd. and I-contg. formulations presented. Thus, Na (3R,5R)-3,5-dihydroxy-7-[(1S,2S,6S,8S,8aR)-6-hydroxy-2-methyl-8-(2-ethyl-2-methylbutyryloxy)-1,2,6,7,8,8a-hexahydro-1-naphthyl]heptanoate was prepd. and demonstrated IC50 against HMG-CoA reductase of a 33.8 nM, and ED50 sterol-synthesis inhibitory activity in mouse liver of 0.063 mg/kg.

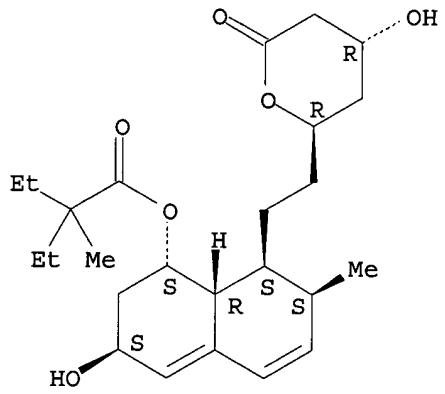
IT **159224-88-1P 159224-89-2P 159224-90-5P**
159224-91-6P 159224-92-7P 159224-93-8P
159224-94-9P 159224-95-0P 159224-96-1P
159224-97-2P 159224-98-3P 159224-99-4P
159225-00-0P 159225-01-1P 159225-02-2P

Golam Shameem

159225-03-3P 159225-04-4P 159225-05-5P
159225-06-6P 159225-07-7P 159225-08-8P
159225-09-9P 159345-65-0P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of hexahydronaphthyl ester anticholesteremics)

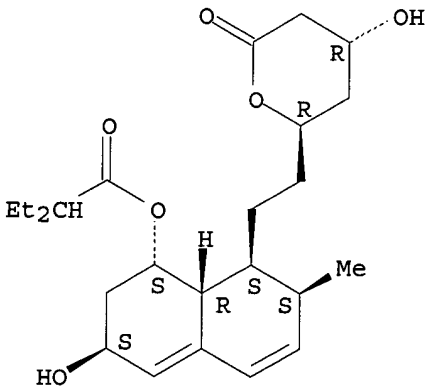
RN 159224-88-1 CAPLUS
CN Butanoic acid, 2-ethyl-2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



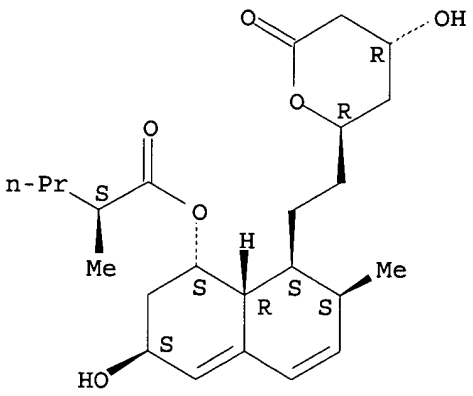
RN 159224-89-2 CAPLUS
CN Butanoic acid, 2-ethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



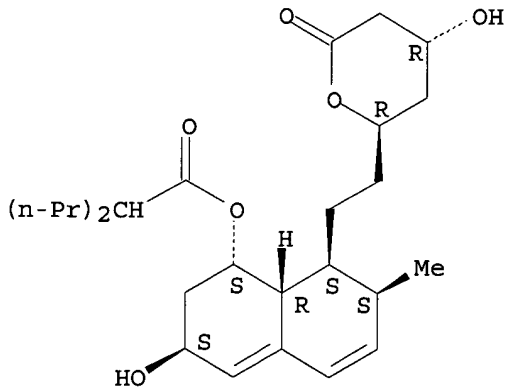
RN 159224-90-5 CAPLUS
CN Pentanoic acid, 2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



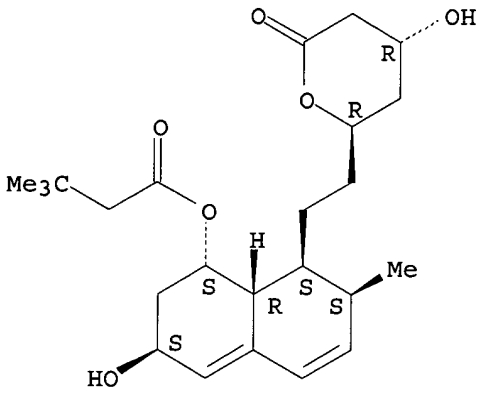
RN 159224-91-6 CAPLUS
CN Pentanoic acid, 2-propyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



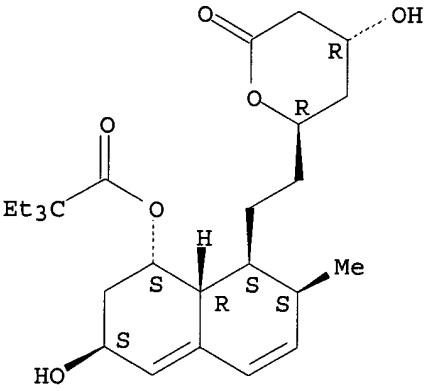
RN 159224-92-7 CAPLUS
CN Butanoic acid, 3,3-dimethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



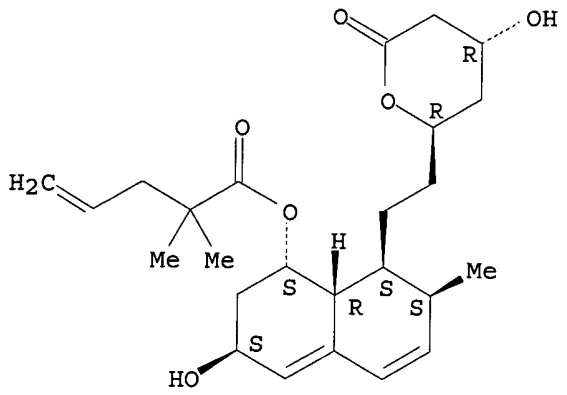
RN 159224-93-8 CAPLUS
CN Butanoic acid, 2,2-diethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



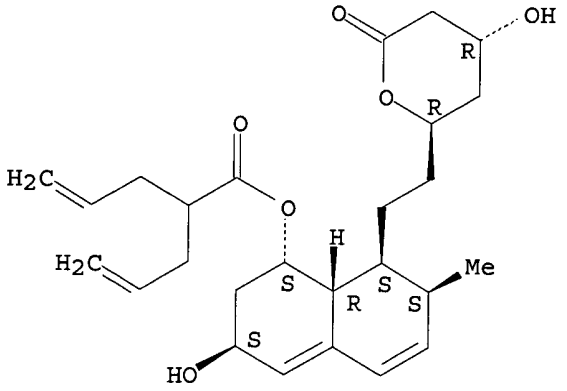
RN 159224-94-9 CAPLUS
CN 4-Pentenoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



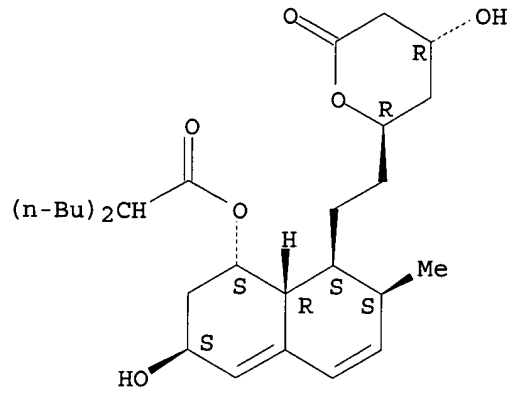
RN 159224-95-0 CAPLUS
CN 4-Pentenoic acid, 2-(2-propenyl)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



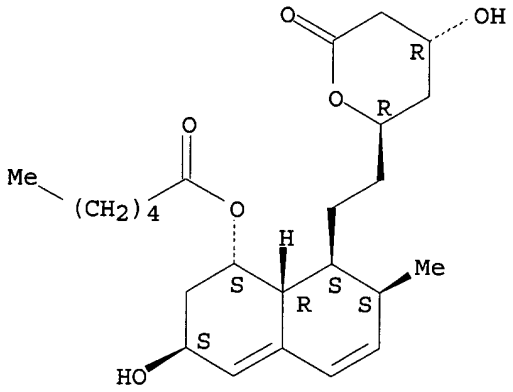
RN 159224-96-1 CAPLUS
CN Hexanoic acid, 2-butyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



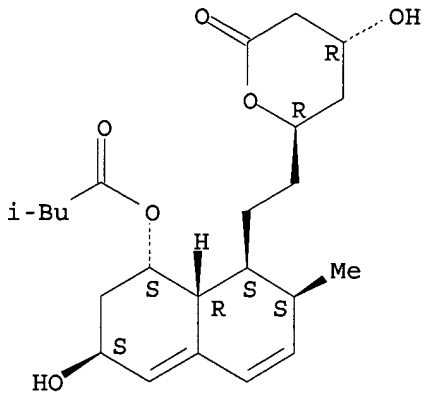
RN 159224-97-2 CAPLUS
CN Hexanoic acid, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



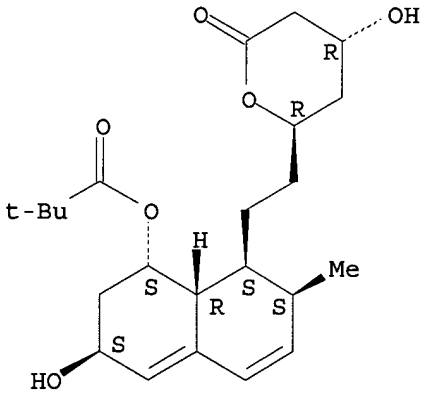
RN 159224-98-3 CAPLUS
CN Butanoic acid, 3-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



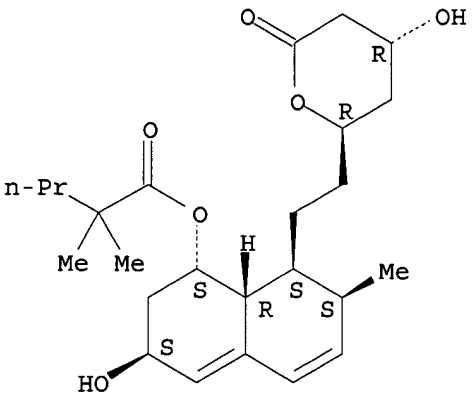
RN 159224-99-4 CAPLUS
CN Propanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



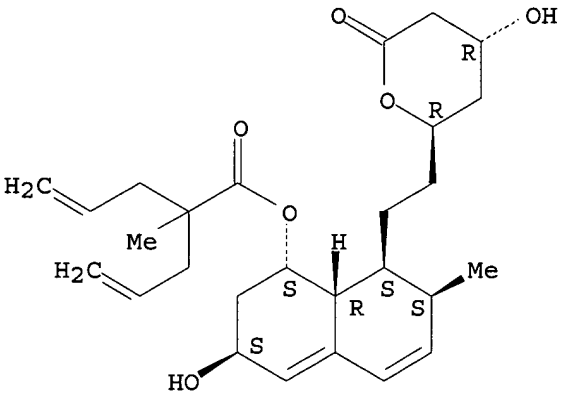
RN 159225-00-0 CAPLUS
CN Pentanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



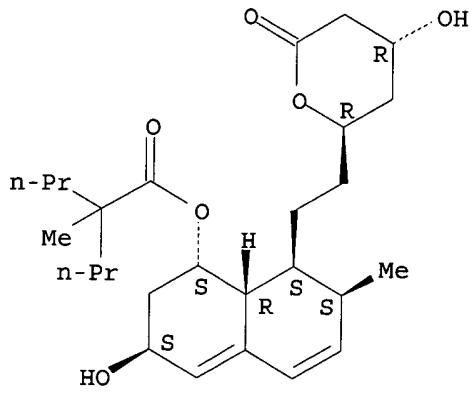
RN 159225-01-1 CAPLUS
CN 4-Pentenoic acid, 2-methyl-2-(2-propenyl)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



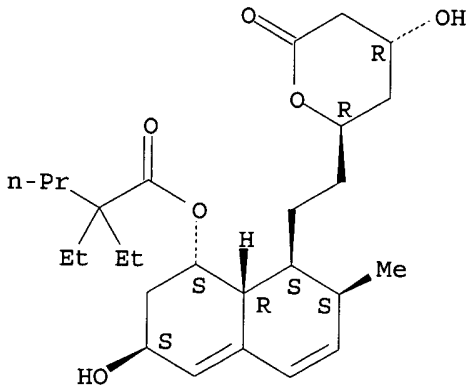
RN 159225-02-2 CAPLUS
CN Pentanoic acid, 2-methyl-2-propyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



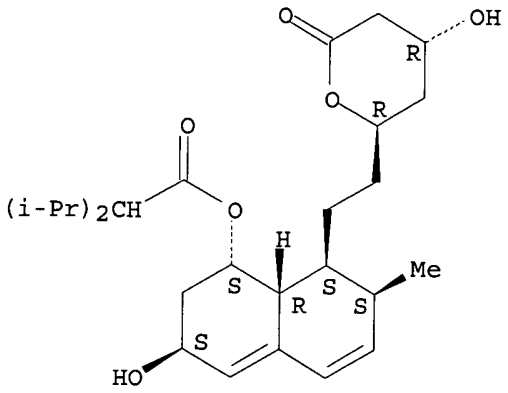
RN 159225-03-3 CAPLUS
CN Pentanoic acid, 2,2-diethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



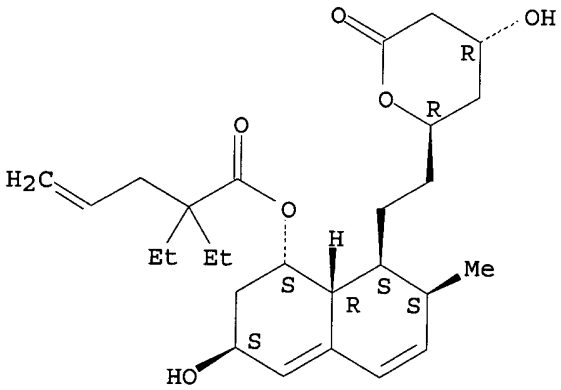
RN 159225-04-4 CAPLUS
CN Butanoic acid, 3-methyl-2-(1-methylethyl)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



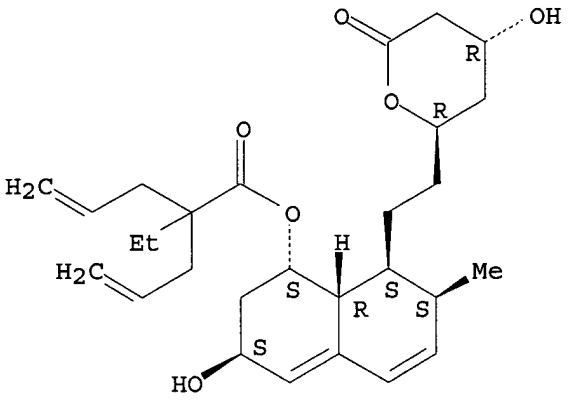
RN 159225-05-5 CAPLUS
CN 4-Pentenoic acid, 2,2-diethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



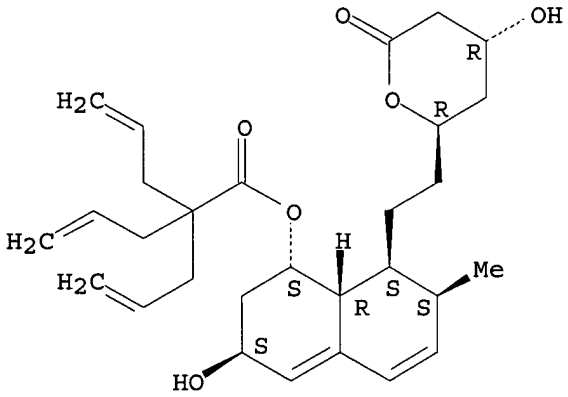
RN 159225-06-6 CAPLUS
CN 4-Pentenoic acid, 2-ethyl-2-(2-propenyl)-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

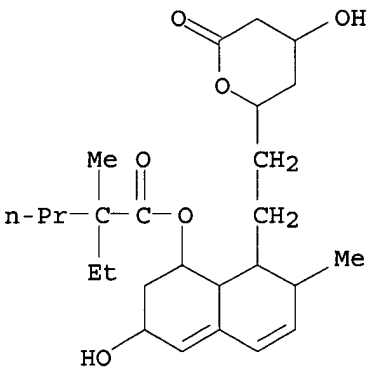


RN 159225-07-7 CAPLUS
CN 4-Pentenoic acid, 2,2-di-2-propenyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

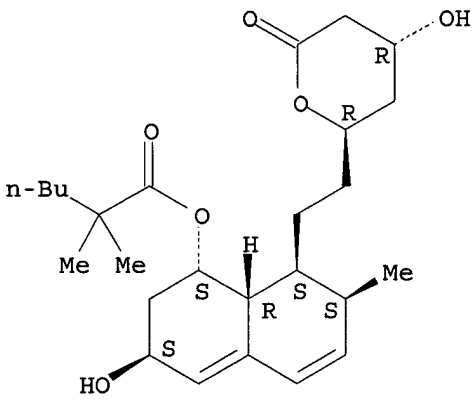


RN 159225-08-8 CAPLUS
CN Pentanoic acid, 2-ethyl-2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)



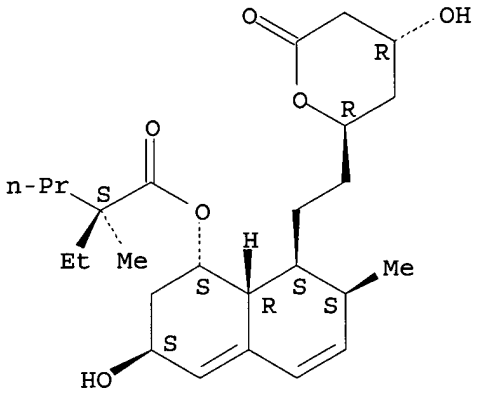
RN 159225-09-9 CAPLUS
CN Hexanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



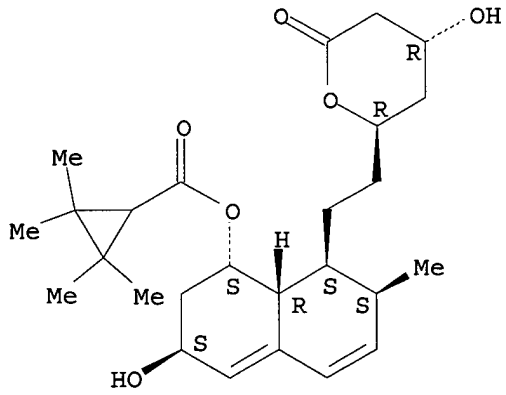
RN 159345-65-0 CAPLUS
CN Pentanoic acid, 2-ethyl-2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(R*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



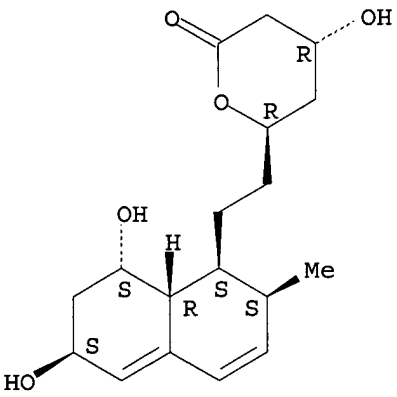
IT **159225-42-0P 159345-93-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of hexahydronaphthyl ester anticholesteremics)
RN 159225-42-0 CAPLUS
CN Cyclopropanecarboxylic acid, 2,2,3,3-tetramethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 159345-93-4 CAPLUS
CN 2H-Pyran-2-one, 6-[2-(1,2,6,7,8,8a-hexahydro-6,8-dihydroxy-2-methyl-1-naphthalenyl)ethyl]tetrahydro-4-hydroxy-, [1S-[1.alpha.(2S*,4S*),2.alpha.,6.alpha.,8.beta.,8a.alpha.]]- (9CI) (CA INDEX NAME)

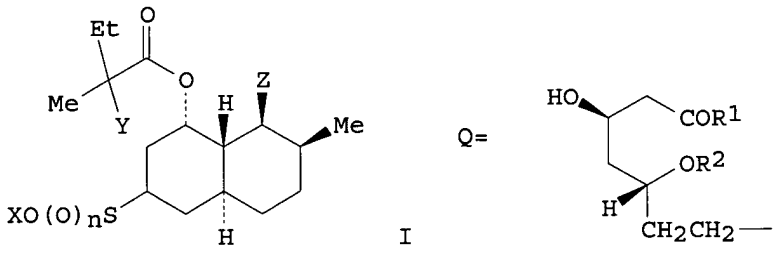
Absolute stereochemistry.



L7 ANSWER 33 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:508373 CAPLUS
DOCUMENT NUMBER: 121:108373
TITLE: Preparation of sulfomevinolinates and analogs as HMG-CoA reductase inhibitors
INVENTOR(S): Poss, Kathleen M.
PATENT ASSIGNEE(S): Squibb, E. R., and Sons, Inc., USA
SOURCE: U.S., 7 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5286746	A	19940215	US 1991-811124	19911220

OTHER SOURCE(S): MARPAT 121:108373
GI



I

AB Title compds. [I; X = H, alkali metal, ammonium; Y = H, (cyclo)alkyl, aryl(alkyl); Z = heptanoate group Q; R1 = OH, alkoxy, ONa, etc.; R2 = H; R1R2 = bond] were prepd. as HMG-CoA reductase inhibitors (no data). Thus, [1s-[1.alpha.(R*),3.beta.,4.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]-2-methylbutanoic acid 3-hydroxy-1,2,3,7,8,8a-hexahydro-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthyl ester was converted in 9 steps to Me [1S-[1.alpha.(.beta.S*, .DELTA.S*),2.alpha.,4a.beta.,6.beta.,8.beta.,8a.alpha.]]-8-(2,2-dimethyl-1-oxobutoxy)decahydro-.beta.,.DELTA.-dihydroxy-2-methyl-6-sulfo-1-

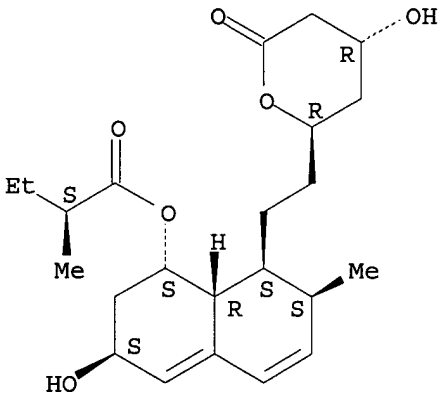
naphthaleneheptanoate.

IT **85956-22-5**
RL: RCT (Reactant)
(reaction of, in prepn. of HMG-CoA reductase inhibitor)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 34 OF 69 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1994:68838 CAPLUS

DOCUMENT NUMBER: 120:68838

TITLE: Hepatoselective carrier-mediated sodium-independent uptake of pravastatin and pravastatin-lactone

AUTHOR(S): Ziegler, Kornelia; Hummelsiep, Silke

CORPORATE SOURCE: Institut fuer Pharmakologie und Toxikologie der Justus-Liebig Universitaet, Frankfurterstr. 107, Giessen, 35392, Germany

SOURCE: Biochim. Biophys. Acta (1993), 1153(1), 23-33
CODEN: BBACAQ; ISSN: 0006-3002

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Pravastatin and pravastatin-lactone are not taken up into extrahepatic cells such as fibroblasts, or hepatoma cells such as AS-30D ascites hepatoma cells or FAO cells. In contrast, pravastatin is taken up into isolated rat hepatocytes by a carrier mediated, saturable, temp.-dependent and energy-dependent mechanism. The kinetic parameters for the saturable uptake are Km 27 .mu.M, Vmax 537 pmol/mg per min. The permeability coeffs. were detd. to be 9.829.cntdot.10-7 cm/s at 4.degree.C, 1.76.cntdot.10-6 cm/s at 7.degree.C, 3.85.cntdot.10-6 cm/s at 17.degree.C and 5.82.cntdot.10-6 cm/s at 37.degree.C. The activation energy is 60 kJ/mol for 100 .mu.M pravastatin at 37.degree.C. The Q10 values are between 1.7 and 2.8. In the presence of metabolic inhibitors and in the absence of oxygen, transport is inhibited. Uptake of pravastatin is not dependent on an extracellular to intracellular sodium-gradient. Replacement of chloride by sulfate, nitrate, gluconate or thiocyanate significantly inhibits the uptake of pravastatin. Uptake is competitively inhibited by cholate and taurocholate in the presence and absence of sodium. Pravastatin, however, competitively inhibits the uptake of cholate and taurocholate only in the absence of sodium. In addn., pravastatin-lactone enters liver cells via an energy-dependent,

carrier-mediated uptake system. For the saturable energy-dependent part of the hepatocellular uptake a Km value of 9 .mu.M and a Vmax value of 621 pmol/mg per min was detd. The permeability coeff. of pravastatin-lactone uptake is calcd. to be 5.41.cntdot.10-6 cm/s at 37.degree.C. The uptake of pravastatin-lactone is competitively-noncompetitively inhibited by pravastatin and by lovastatin and vice versa. These results indicate that the hepatoselectivity of pravastatin is due to its carrier-mediated uptake into rat hepatocytes via a sodium-independent bile acid carrier. Pravastatin-lactone resembles pravastatin-sodium in its hepatoselectivity.

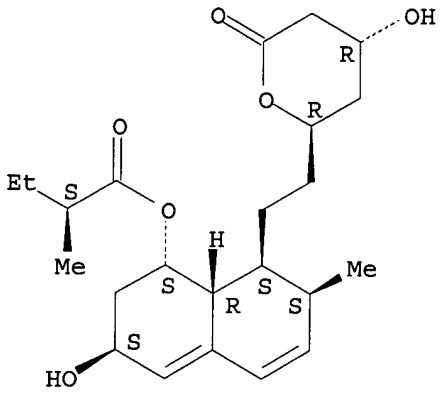
IT **143289-89-8**, Pravastatin lactone
RL: PROC (Process)
(carrier-mediated uptake of, by hepatocytes)
RN 143289-89-8 CAPLUS

L7 ANSWER 35 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:530802 CAPLUS
DOCUMENT NUMBER: 119:130802
TITLE: Studies on drug metabolism using LC/MS (II). Analysis of cholesterol-lowering agents and the related analogs
AUTHOR(S): Iwabuchi, Haruo; Kitazawa, Eiichi; Watanabe, Hidetoshi; Kobayashi, Nobuhiro; Nakamura, Kanichi; Kanai, Michiko
CORPORATE SOURCE: Anal. Lab., Sankyo Co., Ltd., Japan
SOURCE: Nippon Iyo Masu Supekutoru Gakkai Koenshu (1991), 16, 153-6
CODEN: NIMKEN; ISSN: 0916-085X
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB Three ionization methods of LC/MS(APCI, TSP and ESI) were characterized by investigating the relationships between sensitivities and polarities of the compds. LogP values and MS of 13 compds. including three HMG-CoA reductase inhibitors, their metabolites and the related compds., were measured. Their LogP values were ranging from -2.49 to 4.40, and in LC/MS, each of the ionization methods gave different quasi-mol. ions and sensitivities. The APCI method showed the high sensitivity of several nanograms for hydrophobic compds.(LogP > 2), but was not effective for hydrophilic compds., such as glutathione conjugate. TSP method was found to be applicable to all compds. used in this study, and more sensitive for hydrophobic compds. ESI method was also applicable to all compds. (up to 20 ng), and was 10-100 times more sensitive than the other methods in the case of hydrophilic compds. Addn. of ammonium acetate in LC mobile phase increased the sensitivities in both APCI and TSP methods.

IT **85956-22-5**, R 414
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, by liq. chromatog./mass spectrometry)
RN 85956-22-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

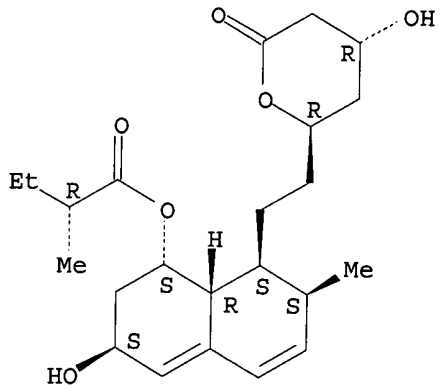


L7 ANSWER 36 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:160467 CAPLUS
DOCUMENT NUMBER: 118:160467
TITLE: Disposition and metabolism of pravastatin sodium in rats, dogs and monkeys
AUTHOR(S): Komai, T.; Kawai, K.; Tokui, T.; Tokui, Y.; Kuroiwa, C.; Shigehara, E.; Tanaka, M.
CORPORATE SOURCE: Anal. Metab. Res. Lab., Sankyo Co. Ltd., Tokyo, Japan
SOURCE: Eur. J. Drug Metab. Pharmacokinet. (1992), 17(2), 103-13
CODEN: EJDPD2; ISSN: 0398-7639
DOCUMENT TYPE: Journal
LANGUAGE: English

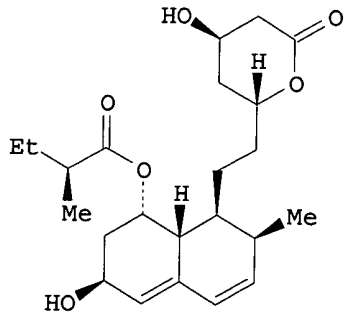
AB Pravastatin sodium (pravastatin) is a potent inhibitor of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase, and was found to be highly effective in animals and humans, in lowering the plasma cholesterol level by inhibiting cholesterol synthesis selectively in the liver. In the present study the disposition and metab. of pravastatin was studied in rats, dogs and monkeys using [14C]-labeled compd. The extent of absorption was approx. 70% in rats and 50% in dogs. Tissue distribution examd. by both whole-body autoradiog. and radioactivity measurement demonstrated that the drug was selectively taken up by the liver, a target organ of the drug, and excreted via bile mainly in unchanged form. Since pravastatin excreted by the bile was reabsorbed, the enterohepatic circulation maintained the presence of unchanged pravastatin in the target organ. The profiles of metabolites were studied in various tissues and excreta and a metabolic pathway of pravastatin was proposed.

IT **81093-38-1**
RL: FORM (Formation, nonpreparative)
(formation of, as pravastatin metabolite)
RN 81093-38-1 CAPLUS
CN Butanoic acid, 2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

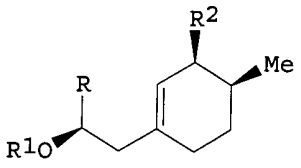
Absolute stereochemistry.



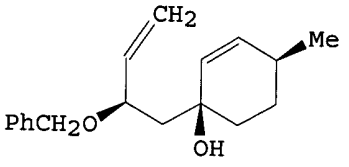
L7 ANSWER 37 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:651102 CAPLUS
DOCUMENT NUMBER: 117:251102
TITLE: Remote diastereoselection in the asymmetric synthesis of pravastatin
AUTHOR(S): Daniewski, A. R.; Wovkulich, P. M.; Uskokovic, M. R.
CORPORATE SOURCE: Roche Res. Cent., Hoffmann-La Roche, Inc., Nutley, NJ, 07110, USA
SOURCE: J. Org. Chem. (1992), 57(26), 7133-9
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



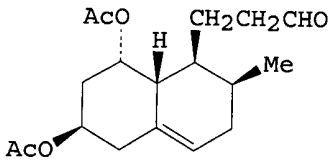
I



II



III



IV

AB The first total synthesis of pravastatin (I) is described. The desymmetrization of 1-methyl-4-methylenecyclohexane by an asym. ene reaction to form cyclohexene II (R =CO2Me, R1, R2 = H) provided the initial asym. framework. The remaining stereogenic centers were introduced sequentially by a series of diastereoselective processes which include the iodolactonization of II (R =CO2Me, R1, R2 = H), the

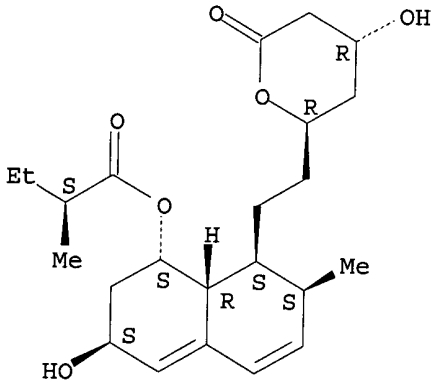
Eschenmoser-Claisen rearrangement of cyclohexenol III, the stereoselective intramol. ene reaction of II (R = CH2CHO, R1 = CH2Ph, R2 = CH2CONMe2), and the diastereoselective condensation of aldehyde IV with Me3SiOC(:CH2)CH:CHOMe.

IT **85956-22-5P**
RL: RCT (Reactant); PREP (Preparation)
(stereoselective total synthesis of)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 38 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:563312 CAPLUS
DOCUMENT NUMBER: 117:163312
TITLE: Metabolism of pravastatin sodium in isolated rat hepatocytes. I. Glutathione conjugate formation reaction
AUTHOR(S): Muramatsu, S.; Miyaguchi, K.; Iwabuchi, H.; Matsushita, Y.; Nakamura, T.; Kinoshita, T.; Tanaka, M.; Takahagi, H.
CORPORATE SOURCE: Anal. Res. Lab., Sankyo Co., Ltd., Tokyo, 140, Japan
SOURCE: Xenobiotica (1992), 22(5), 487-98
CODEN: XENOBH; ISSN: 0049-8254
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The metabolic fate of pravastatin was studied in isolated rat hepatocytes. Two polar metabolites were isolated and identified as a glutathione conjugate and a dihydrodiol. Both metabolites were formed via an epoxide which has been identified as the 4'a.beta.,5'.beta.-epoxide on the decalin moiety. Formation of the glutathione conjugate was enzymic, while the dihydrodiol was formed by nonenzymic hydrolysis of the epoxide accompanied by the intramol. migration of the double bond.

IT **143289-89-8**, Pravastatin lactone
RL: BIOL (Biological study)
(epoxidn. and protection of)

RN 143289-89-8 CAPLUS

L7 ANSWER 39 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:407739 CAPLUS
DOCUMENT NUMBER: 117:7739

TITLE: Mevinic acid derivatives useful as antihypercholesterolemic agents and method for preparing same

INVENTOR(S): Saunders, Jeffrey O.; Gordon, Eric M.
PATENT ASSIGNEE(S): Squibb, E. R., and Sons, Inc., USA

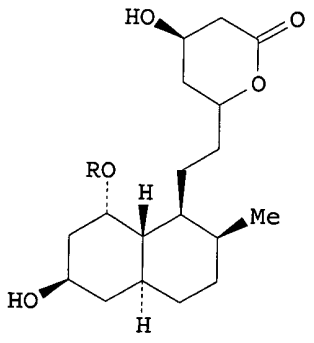
SOURCE: U.S., 11 pp. Cont. of U.S. Ser. No. 431,263, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5099035	A	19920324	US 1991-662597	19910301
US 5166364	A	19921124	US 1991-765806	19910926

PRIORITY APPLN. INFO.: US 1989-316203 19890227
US 1989-431263 19891103
US 1991-662597 19910301

OTHER SOURCE(S): MARPAT 117:7739

GI



I

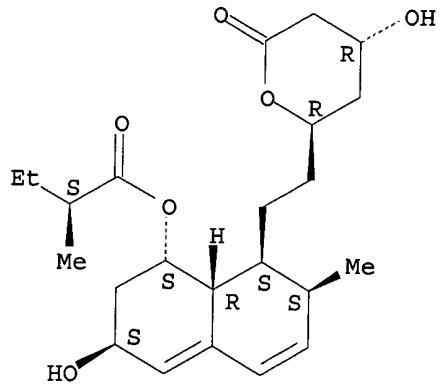
AB The ester I (R = EtCMe2CO) was prepd. from I [R = (S)-EtCHMeCO] by hydrolysis, relactonization, silylation, esterification, and deprotection. I [R = (S)-EtCHMeCO] was prepd. from pravastatin by lactonization, and redn.

IT **85956-22-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and silylation of)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

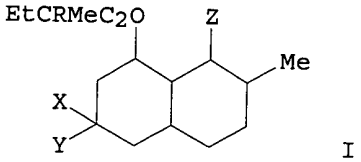
Absolute stereochemistry.



L7 ANSWER 40 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:235347 CAPLUS
DOCUMENT NUMBER: 116:235347
TITLE: Sulfur-substituted mevinic acid derivatives
INVENTOR(S): Varma, Ravi K.; Saunders, Jeffrey O.; Chao, Sam T.; Gordon, Eric M.; Santafianos, Dinos P.
PATENT ASSIGNEE(S): Squibb, E. R., and Sons, Inc., USA
SOURCE: Eur. Pat. Appl., 73 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 465265	A1	19920108	EP 1991-306125	19910705
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
US 5264455	A	19931123	US 1991-724272	19910701
AU 9180120	A1	19920109	AU 1991-80120	19910703
AU 647492	B2	19940324		
ZA 9105171	A	19920624	ZA 1991-5171	19910703
CA 2046171	AA	19920107	CA 1991-2046171	19910704
NO 9102636	A	19920107	NO 1991-2636	19910705
FI 9103285	A	19920107	FI 1991-3285	19910705
HU 58682	A2	19920330	HU 1991-2287	19910705
JP 04230357	A2	19920819	JP 1991-165683	19910705
RU 2041205	C1	19950809	RU 1991-5001316	19910705
CN 1058585	A	19920212	CN 1991-105317	19910706

PRIORITY APPLN. INFO.: US 1990-549024 19900706
OTHER SOURCE(S): MARPAT 116:235347
GI



I

Golam Shameem

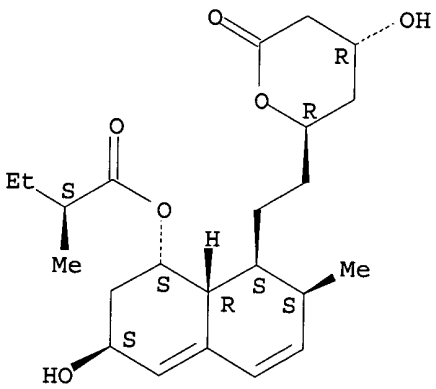
AB Title compds. I [X = H, R1(O)mS wherein R1 = H, acyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, etc.; m = 0-2; Y = H, R2(O)nS wherein R2 = R1; n = m; X and Y are not both H; one of X and Y is HS-alkylene-S and the other is H; Z = R3O2CCH2CH(OH)CH2CH(OH)CH2CH2 wherein R3 = H, alkyl, NH4, alkylammonium, alkali metal, 2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl] and salts thereof, useful as antihypercholesterolemic agents (no data), are prepd. For example, [1S-[1.alpha.(R),3.beta.,4.beta.,7.beta.,8.beta.(2S,4S),8a.beta.]]-3-Hydroxy-1,2,3,7,8,8a-hexahydro-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate was converted in 8 steps to [1S-[1.alpha.,4a.alpha.,7.beta.,8.beta.(2S,4S),8a.beta.]]-3,3-bis(methylthio)decahydro-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2,2-dimethylbutanoate.

IT **85956-22-5**
RL: RCT (Reactant)
(reaction of, in prepn. of antihypercholesterolemics)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 41 OF 69 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1992:188050 CAPLUS

DOCUMENT NUMBER: 116:188050

TITLE: EIA of pravastatin in blood

INVENTOR(S): Muramatsu, Shigeki; Takasaki, Wataru; Takahagi, Hidekuni

PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 03289564	A2	19911219	JP 1990-91292	19900405

AB A method for detg. pravastatin in blood involves: reacting test pravastatin in a sample with enzyme (peroxidase)-labeled

Golam Shameem

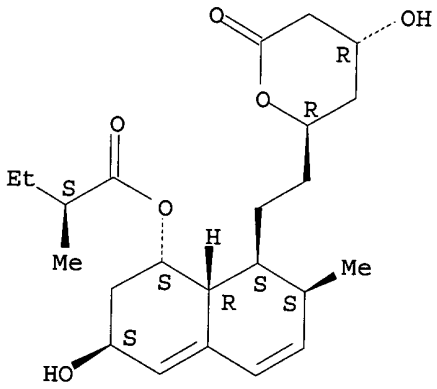
5-dehydroxypravastatin and anti-5-dehydroxypravastatin antibody, sepg. bound label from free label, and detg. the label activity to det. test pravastatin in the sample using a std. curve. The detection range was 600 pg-200 ng/mL. This competitive EIA is simple and specific. Prepn. of 5-dehydroxypravastatin-bovine serum albumin complex for antibody prodn. is described.

IT **85956-22-5**
RL: RCT (Reactant)
(reaction of, for dehydroxypravastatin-bovine serum albumin complex prepn.)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

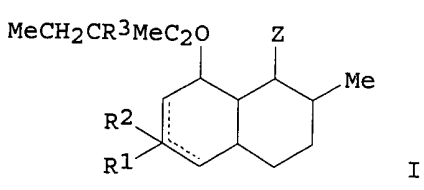
Absolute stereochemistry.



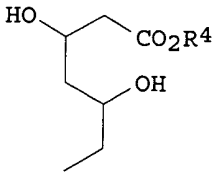
L7 ANSWER 42 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:83449 CAPLUS
DOCUMENT NUMBER: 116:83449
TITLE: Preparation of fluorinated derivatives of mevinic acids as antihypercholesteremics
INVENTOR(S): Varma, Ravi K.; Chao, Sam T.; Gordon, Eric M.
PATENT ASSIGNEE(S): Squibb, E. R., and Sons, Inc., USA
SOURCE: Eur. Pat. Appl., 20 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 456214	A1	19911113	EP 1991-107487	19910508
R: DE, FR, GB, IT				
US 5089523	A	19920218	US 1990-521880	19900511
CA 2040530	AA	19911112	CA 1991-2040530	19910416
JP 04226941	A2	19920817	JP 1991-105616	19910510

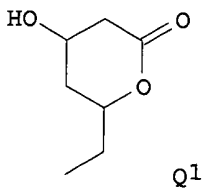
PRIORITY APPLN. INFO.: US 1990-521880 19900511
OTHER SOURCE(S): MARPAT 116:83449
GI



I



Q



Q1

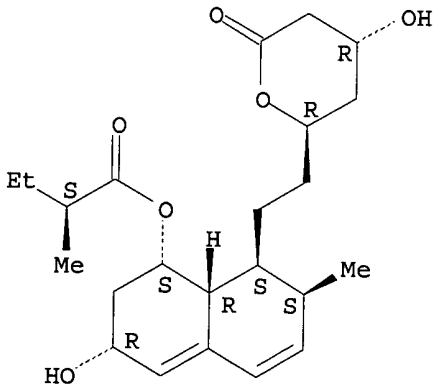
AB Title compds. I (R1, R2 = F, H .gtoreq.1 of R1 and R2 = F; R3 = H, alkyl, cycloalkyl, aryl, arylalkyl; Z = Q, Q1; R4 = H, H3N+, alkyl, alkylammonium, alkali metal) useful as antihypercholesteremics (no data) are prepd. [1S-[1.alpha.(R),3.beta.,4.beta.,7.beta.,8.beta.(2S,4S,8A.beta.]]-2-methylbutanoic acid 3-hydroxy-1,2,3,7,8,8a-hexahydro-7-methyl-8-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester was converted in 7 steps to [1S[1.alpha.,4a.alpha.,7.beta.,8.beta.(2S,4S),8a.beta.]]-I (R1 = R2 = F, R3 = H, Z = Q1). I are also useful for inhibiting or treating atherosclerosis (no data) and a pharmaceutical compn. comprises I.

IT **85956-23-6**
RL: RCT (Reactant)
(reaction of, in prepn. of antihypercholesteremic agents)

RN 85956-23-6 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 43 OF 69 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1992:57414 CAPLUS

DOCUMENT NUMBER: 116:57414

TITLE: Bioconversion of the sodium salt of Simvastatin (MK-733) to 6-desmethyl-6-.alpha.-hydroxymethyl Simvastatin

AUTHOR(S): Marcin, C.; White, R.; Hirsch, C.; Ferris, F.; Sykes, R.; Houck, D.; Greasham, R.; Chartrain, M.

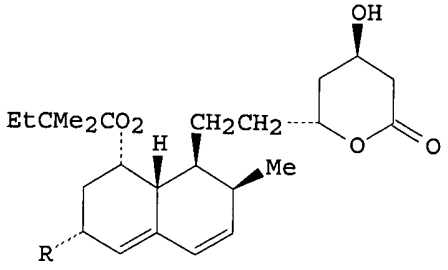
CORPORATE SOURCE: Merck Sharp and Dohme Res. Lab., Rahway, NJ, 07065, USA

SOURCE: J. Ind. Microbiol. (1991), 8(3), 157-64
CODEN: JIMIE7; ISSN: 0169-4146

DOCUMENT TYPE: Journal

Golam Shameem

LANGUAGE: English
GI



I, R=Me
II, R=$HOCH_2$

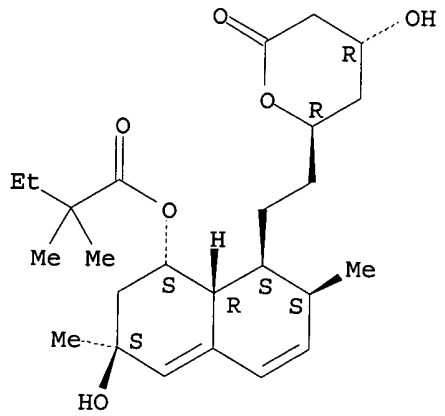
AB An actinomycete (MA 6474, ATCC 53828) isolated from a soil sample transformed the Na salt of Simvastatin (MK-733, I) to 6-.alpha.-hydroxymethyl MK-733 (II), 6-.beta.-hydroxymethyl MK-733, and 6-ring-hydroxy MK-733. The bioconversion efficiency to the desired compd., II, was enhanced by optimizing the physicochem. parameters of the process. In shake flask cultures, addn. of Mg resulted in a 5-fold increase in the rate of conversion of I to II. The ratio of bioconversion products was regulated by pH. Process improvements and scale up in 23-L fermentors, which consisted of a controlled addn. of substrate (I), resulted in a 2-fold increase in II prodn. (42 vs. 79 U/mL) and a 23-fold rate increase in the formation of II. A high diastereomeric ratio (.alpha.:.beta. = 9:1) facilitated downstream processing.

IT **129464-60-4**
RL: FORM (Formation, nonpreparative)
(formation of, from simvastatin by actinomycete)

RN 129464-60-4 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 44 OF 69 CAPLUS COPYRIGHT 2001 ACS

Golam Shameem

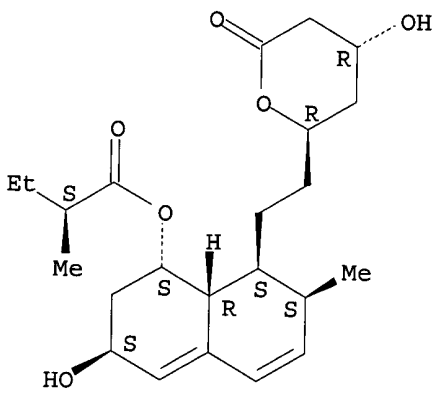
ACCESSION NUMBER: 1991:669981 CAPLUS
DOCUMENT NUMBER: 115:269981
TITLE: Relative lipophilicities, solubilities, and structure-pharmacological considerations of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors pravastatin, lovastatin, mevastatin, and simvastatin
AUTHOR(S): Serajuddin, Abu T. M.; Ranadive, Sunanda A.; Mahoney, Eileen M.
CORPORATE SOURCE: Bristol-Myers Squibb Pharm. Res. Inst., New Brunswick, NJ, 08903, USA
SOURCE: J. Pharm. Sci. (1991), 80(9), 830-4
CODEN: JPMSAE; ISSN: 0022-3549
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The apparent octanol-water partition coeffs. (Po/w) and aq. solubilities for four 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors [pravastatin, lovastatin (mevinolin), mevastatin (compactin), and simvastatin (synvinolin)] were compared. Pravastatin is highly hydrophilic compared with lovastatin, mevastatin, or simvastatin. Pravastatin is clin. used as the active hydroxy acid, while the other three compds. are administered as prodrug lactones which, over a period of time, convert in vivo to their resp. active hydroxy acid forms. The order of the Po/w values of the hydroxy acid forms was pravastatin .mchlt. mevastatin < lovastatin < simvastatin at each pH evaluated, with approx. ratios of 1:25:75:200, resp. The relative order and the ratios of partition coeffs. for the lactone forms were similar to those for the hydroxy acid forms. In addn., lovastatin, mevastatin, and simvastatin are virtually insol. in water, with soly. values ranging from 0.0013 to 0.0015 mg/mL at 23.degree.. In comparison, paravastatin is hydrophilic, as demonstrated by the >100-fold greater soly. of its lactone form (0.18 mg/mL). The greater hydrophilicity of paravastatin may explain its reported lower permeation into nonhepatic cells and the selectivity with respect to inhibition of cholesterol synthesis.

IT **85956-22-5**
RL: BIOL (Biological study)
(partition and soly. of, structure effect on, as hydroxymethylglutaryl-CoA reductase inhibitor)

RN 85956-22-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



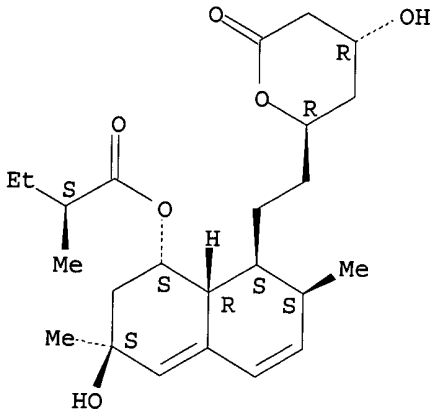
Golam Shameem

L7 ANSWER 45 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:669871 CAPLUS
DOCUMENT NUMBER: 115:269871
TITLE: Biotransformation of lovastatin. IV. Identification of cytochrome P4503A proteins as the major enzymes responsible for the oxidative metabolism of lovastatin in rat and human liver microsomes
AUTHOR(S): Wang, Regina W.; Kari, Prasad H.; Lu, Anthony Y. H.; Thomas, Paul E.; Guengerich, F. Peter; Vyas, Kamlesh P.
CORPORATE SOURCE: Dep. Anim. Explor. Drug Metab., Merck Sharp and Dohme Res. Lab., Rahway, NJ, 07065, USA
SOURCE: Arch. Biochem. Biophys. (1991), 290(2), 355-61
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English

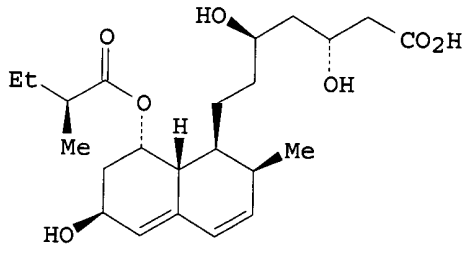
AB Previous studies have shown that the metab. of the cholesterol-lowering drug lovastatin by rat and human liver microsomes occurs primarily at the 6'-position, giving 6'.beta.-hydroxy- and 6'-exomethylene-lovastatin and that these oxidns. are catalyzed by cytochrome P 450-dependent monooxygenases. In the present study, the specific cytochrome P 450 form involved in lovastatin oxidn. was identified through immunoinhibition studies. Among several antibodies prepd. against various cytochrome P450s, only anti-rat P 4503A IgG inhibited lovastatin metab. in liver microsomes from untreated, phenobarbital-treated, and pregnenolone-16.alpha.-carbonitrile-treated rats. Lovastatin metab. at the 6'-position was markedly inhibited (6'.beta.-hydroxy, greater than 95%; 6'-exomethylene, 70-80%) by this antibody whereas the effect of anti-rat P 4503A on the 3'-hydroxylation was variable depending on the source of the microsomes. With human liver microsomes, both anti-rat P 4503A and anti-human P 4503A inhibited lovastatin metab. Correlation between lovastatin oxidn. and the P 4503A content in human liver microsomes (measured by immunoblot anal.) was excellent. In addn., preincubation of human liver microsomes with troleandomycin and NADPH inhibited metab. by 60%. These results clearly indicate that cytochrome P 4503A enzymes are primarily responsible for the metab. of lovastatin in rat and human liver microsomes.

IT **125638-71-3**
RL: FORM (Formation, nonpreparative)
(formation of, by liver microsomes as lovastatin metabolite in humans and lab. animals)
RN 125638-71-3 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

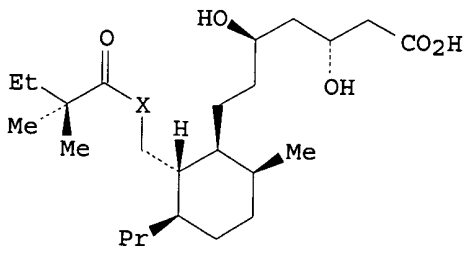
Absolute stereochemistry.



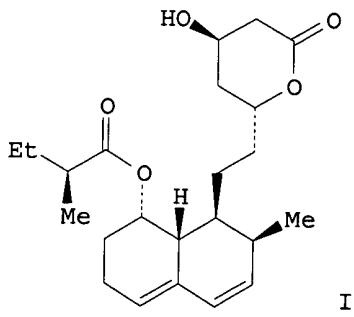
L7 ANSWER 46 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:583616 CAPLUS
DOCUMENT NUMBER: 115:183616
TITLE: Synthetic transformations of the mevinic acid nucleus: preparation of a monocyclic analog of compactin
AUTHOR(S): Karanewsky, Donald S.
CORPORATE SOURCE: Bristol-Myers Squibb Pharm. Res. Inst., Princeton, NJ, 08543-4000, USA
SOURCE: Tetrahedron Lett. (1991), 32(32), 3911-14
CODEN: TELEAY; ISSN: 0040-4039
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



II



III

AB The synthetic transformation of pravastatin (I) into a fully functional,

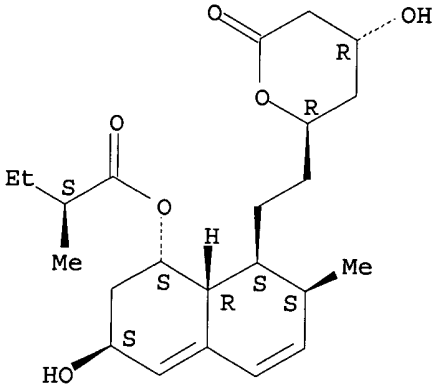
monocyclic analogs II (X = O, NH) of compactin (III) via a multistep sequence is described.

IT **85956-22-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and silylation of, in prepn. of compactin monocyclic analog)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 47 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:514347 CAPLUS
DOCUMENT NUMBER: 115:114347
TITLE: Preparation of secomevinic acid derivatives useful as hypocholesterolemic agents and new intermediates
INVENTOR(S): Karanewsky, Donald S.
PATENT ASSIGNEE(S): Squibb, E. R., and Sons, Inc., USA
SOURCE: Eur. Pat. Appl., 43 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 419856	A2	19910403	EP 1990-116226	19900824
EP 419856	A3	19910807		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
US 5025017	A	19910618	US 1989-413656	19890928
CA 2023857	AA	19910329	CA 1990-2023857	19900823
JP 03130248	A2	19910604	JP 1990-262947	19900928
US 5189180	A	19930223	US 1991-694515	19910501

PRIORITY APPLN. INFO.: US 1989-413656 19890928
OTHER SOURCE(S): MARPAT 115:114347
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

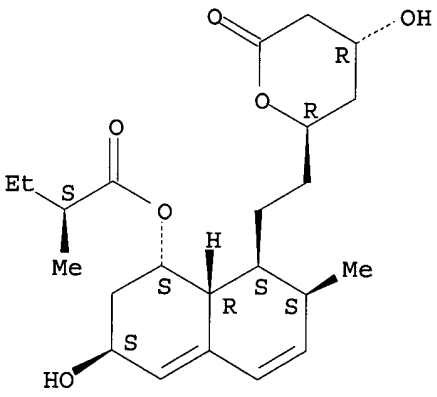
AB Secomevinic acid derivs. [I, II; R = H, alkyl, alkali metal; R1 = H, alkyl, alkoxy, aryl, etc.; R2 = alkyl, cycloalkyl, aralkyl; X = O, S, NR5 wherein R5 = H, alkyl], effective HMG-CoA reductase inhibitors useful as anticholesteremics and antiatherosclerotics, are prepd. To a soln. of Dess-Martin periodinane in CH2Cl2 under Ar were added Me3COH and a soln. of hydroxyethyl deriv. III (R = CH2OH) in CH2Cl2 with stirring at room temp., a soln. of Na2S2O3 in 1N NaHCO3 was added with stirring to give a crude aldehyde III (R3 = CHO), which was oxidized with KMnO4 in Me3COH and 5% NaH2PO4, followed by esterification with CH2N2, to give 77% ester III (R3 = CO2Me) (IV). Hydrolysis of acetonide linkage in IV and lactonization of the hydroxy acid with HF in MeCN gave 98% title compd. I (R1 = Me, R2 = EtCMe2, X = O). The preferred doses are 4-200 mg/day.

IT **85956-22-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction of, in prepn. of anticholesteremic and antiatherosclerotic agent)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

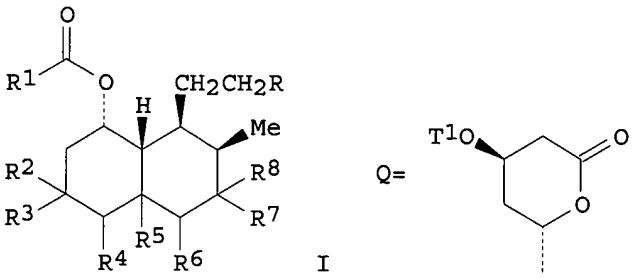
Absolute stereochemistry.



L7 ANSWER 48 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:450029 CAPLUS
DOCUMENT NUMBER: 115:50029
TITLE: Preparation of intermediates for 6-oxosimvastatin analog HMG-CoA reductase inhibitors
INVENTOR(S): Stokker, Gerald E.; Lee, Ta J.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Can. Pat. Appl., 76 pp.
CODEN: CPXXEB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2018481	AA	19901209	CA 1990-2018481	19900607
US 5041562	A	19910820	US 1989-363736	19890609
US 5001241	A	19910319	US 1990-473784	19900202

JP 03115275 A2 19910516 JP 1990-152497 19900611
PRIORITY APPLN. INFO.: US 1989-363736 19890609
US 1990-473784 19900202
OTHER SOURCE(S): MARPAT 115:50029
GI



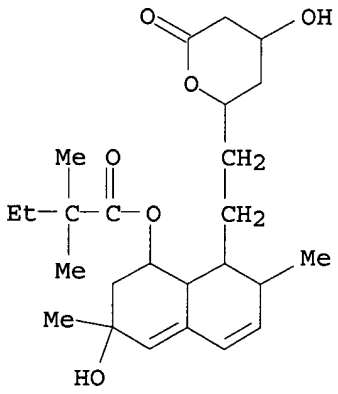
I

AB The title compds. [I; R = tetrahydropyranonyl group Q; R1 = alkoxy, alkenyl, (un)substituted (cyclo)alkyl, Ph, NH2, etc.; R2 = H, Me, CH2OT3; R3R4, R5R6 = bond and R7 = H, R8 = OT2; R3 = H, R8 = OT2 and R4R5, R6R7 = bond; T1-T3 = H, silyl protective group, tetrahydropyranyl] were prepd. Thus, I [R = Q, R1 = EtCMe2, R2 = (R)-Me, R3 = R8 = H, R4R5 = R6R7 = bond] was O-protected and the product converted in 6 steps to I (R = Q, R1 = EtCMe2, R2 = Me, R3R4 = R5R6 = bond, R7R8 = O) which had IC50 of 2 ng/mL against HMG-CoA reductase in vitro.

IT **134523-09-4P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as HMG-CoA reductase inhibitor)

RN 134523-09-4 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)



L7 ANSWER 49 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:429690 CAPLUS
DOCUMENT NUMBER: 115:29690
TITLE: Preparation of 5-oxo analogs of simvastatin as HMG-CoA reductase inhibitors

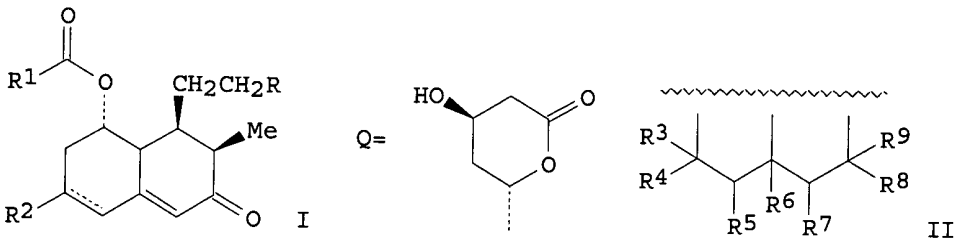
Golam Shameem

INVENTOR(S): Joshua, Henry; Wilson, Kenneth E.; Schwartz, Michael S.; Lee, Ta Jyh; Stokker, Gerald E.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Eur. Pat. Appl., 43 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 409399	A1	19910123	EP 1990-306236	19900608
EP 409399	B1	19960313		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
US 4968693	A	19901106	US 1989-363792	19890609
US 5001241	A	19910319	US 1990-473784	19900202
US 5021453	A	19910604	US 1990-533745	19900606
AT 135352	E	19960315	AT 1990-306236	19900608

PRIORITY APPLN. INFO.: US 1989-363792 19890609
US 1990-473784 19900202
US 1988-162785 19880302
US 1989-363736 19890609

OTHER SOURCE(S): MARPAT 115:29690
GI



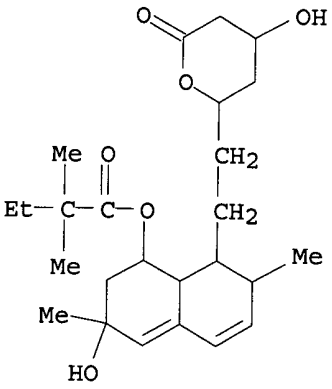
AB The title compds. [I; R = mevalonolactone moiety Q and the corresponding dihydroxy acid analog thereof; R1 = alkoxy, alkenyl, (un)substituted (cyclo)alkyl, Ph, NH2, etc.; R2 = H, Me, CH2OH; dashed line = optional bond] were prepd. Thus, simvastatin was O-protected and the product treated with PhSeCl and H2O2 to give analog II (R = O-protected Q, R1 = CMe2Et) (III; R3 = .alpha.-Me, R4 = R9 = H, R5 = .beta.-Cl, R6 = .alpha.-OH, R7R8 = bond) which was treated with Bu3SnH and the product (R5 = H) oxidized with pyridinium chlorochromate/Al2O3 to give III (R3 = .alpha.-Me, R4 = R5 = H, R6R7 = bond, R8R9 = O). The latter was treated with Et3N and CF3SO3SiMe3 to give III (R3 = .alpha.-Me, R4 = H, R5R6 = R7R8 = bond, R9 = OSiMe3) which was stirred 22 h with Pd(OAc)2 in MeCN/THF to give, after deprotection, I (R = Q, R1 = CMe2Et, R2 = Me, dashed line = bond) (IV). IV had IC50 of 2 ng/mL against HMG-CoA reductase compared with 4.2 ng/mL for simvastatin.

IT **134523-09-4P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as HMG-CoA reductase inhibitor)

RN 134523-09-4 CAPLUS

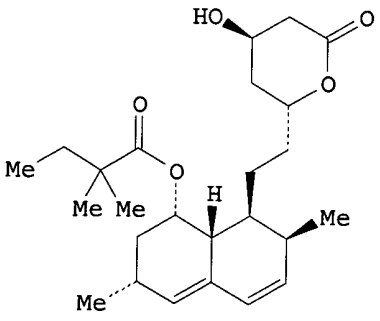
CN Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Golam Shameem



L7 ANSWER 50 OF 69 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1991:427595 CAPLUS
DOCUMENT NUMBER: 115:27595
TITLE: Development of a large-scale continuous substrate feed process for the biotransformation of simvastatin by Nocardia sp.
AUTHOR(S): Gbewonyo, K.; Buckland, B. C.; Lilly, M. D.
CORPORATE SOURCE: Merck Sharp and Dohme Res. Lab., Rahway, NJ, 07065, USA
SOURCE: Biotechnol. Bioeng. (1991), 37(11), 1101-7
CODEN: BIBIAU; ISSN: 0006-3592
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The microbial hydroxylation of simvastatin (I) by a Nocardia sp. is described. I (Zocor) is 1 of the hydroxymethylglutaryl CoA reductase inhibitors used as cholesterol-lowering drugs. Studies at the 14-L scale showed that high I concns. inhibited product formation; consequently, continuous slow feeding was introduced to maintain low residual I concns. Dissolved O2 levels >50% air satn. were desirable for the transformation. The process was scaled up to 19,000-L fermentors using an online filter sterilization system for substrate feeding. The feed rate was regulated by off-line HPLC assays to keep the substrate concn. <20 mg/L. Intermittent addn. of nutrients helped boost the bioconversion rate to give final titers of 400 mg 6-.beta.-hydroxymethylsimvastatin/L.

Golam Shameem

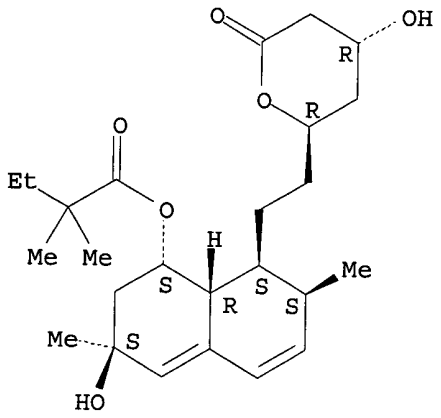
Bioconversion efficiencies of 22-25% with a ratio of desired product/side products of 0.7 were obtained by this process.

IT **129464-60-4**
RL: FORM (Formation, nonpreparative)
(formation of, from simvastatin by Nocardia)

RN 129464-60-4 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 51 OF 69 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1991:199015 CAPLUS

DOCUMENT NUMBER: 114:199015

TITLE: Male-specific metabolism of simvastatin by rat liver microsomes

AUTHOR(S): Uchiyama, Naotaka; Kagami, Yayoi; Saitoh, Yuko; Ohtawa, Masakatsu

CORPORATE SOURCE: Cent. Res. Lab., Banyu Pharm. Co., Ltd., Meguro, 153, Japan

SOURCE: Chem. Pharm. Bull. (1991), 39(1), 236-8
CODEN: CPBTAL; ISSN: 0009-2363

DOCUMENT TYPE: Journal

LANGUAGE: English

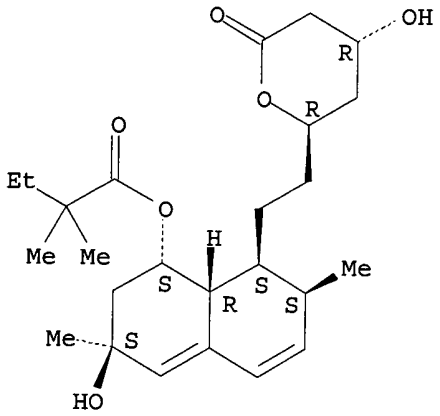
AB Simvastatin was more effectively metabolized by the liver microsomes of male rats than females. The sex difference appeared in the compn. of the metabolites. Two male-specific metabolites were identified by NMR and mass spectrometry as 3''-hydroxy and 3',3''-dihydroxy-.DELTA.4',5' derivs. of simvastatin.

IT **129464-60-4**
RL: FORM (Formation, nonpreparative)
(formation of, as simvastatin metabolite, by liver microsomes, sex differences in)

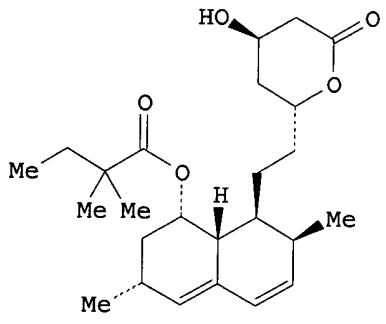
RN 129464-60-4 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 52 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:544802 CAPLUS
DOCUMENT NUMBER: 113:144802
TITLE: In vitro and in vivo biotransformation of simvastatin, an inhibitor of HMG CoA reductase
AUTHOR(S): Vickers, S.; Duncan, C. A.; Vyas, K. P.; Kari, P. H.; Arison, B.; Prakash, S. R.; Ramjit, H. G.; Pitzenberger, S. M.; Stokker, G.; Duggan, D. E.
CORPORATE SOURCE: Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Drug Metab. Dispos. (1990), 18(4), 476-83
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Simvastatin (SV) (I), an analog of lovastatin, is the lactone form of 1',2',6',7',8',8a'-hexahydro-3,5-dihydroxy-2',6'-dimethyl-8'(2'',2''-dimethyl-1''-oxobutoxy)-1'-naphthaleneheptanoic acid (SVA) which lowers plasma cholesterol by inhibiting 3-hydroxy-3-methylglutaryl-CoA reductase. SV but not its corresponding hydroxy acid form SVA underwent microsomal metab. Major in vitro metabolites were 6'-OH-SV and 3''-OH-SV formed by allylic and aliph. hydroxylation, resp., and 6'-exomethylene-SV formed by dehydrogentation. In rats, dogs, and humans, biliary excretion is the major route of elimination. Biliary metabolites (as both hydroxy acids and lactones) also included 6'-CH2OH-SV and 6'-COOH-SV, in both of which

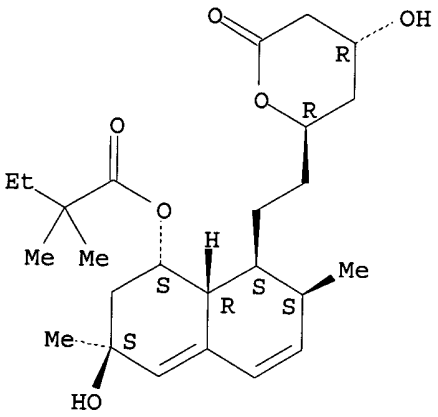
the 6'-chiral center had been inverted. High levels of esterase in rodent plasma favored the formation of SVA from SV. The formation of 1',2',6',7',8',8a'-hexahydro-2',6'-dimethyl-8'-(2'',2''-dimethyl-1-oxobutoxy)-1'-naphthalenepentanoic acid (II) only in rodents represented a species difference in the metab. of SV. It is proposed that II is formed by .beta.-oxidn. pathways of fatty acid intermediary metab. Several metabolites resulting from microsomal oxidn. (after subsequent conversion from lactones to hydroxy acids) are effective inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase and may contribute to the cholesterol lowering effect of SV. Qual., the metab. of SV closely resembles that of lovastatin.

IT **129464-60-4**
RL: FORM (Formation, nonpreparative)
(formation of, as simvastatin metabolite, in liver microsome and bile of humans and lab. animals)

RN 129464-60-4 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 53 OF 69 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1990:434324 CAPLUS

DOCUMENT NUMBER: 113:34324

TITLE: Biotransformation of lovastatin. II. In vitro metabolism by rat and mouse liver microsomes and involvement of cytochrome P-450 in dehydrogenation of lovastatin

AUTHOR(S): Vyas, Kamlesh P.; Kari, Prasad H.; Prakash, Shimoga R.; Duggan, Daniel E.

CORPORATE SOURCE: Dep. Drug Metab., Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA

SOURCE: Drug Metab. Dispos. (1990), 18(2), 218-22
CODEN: DMDSAI; ISSN: 0090-9556

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Metab. of lovastatin, a new cholesterol-lowering drug, by liver microsomes from rats and mice was investigated. Liver microsomes from rats catalyzed biotransformation of lovastatin at a rate of 3 nmol/mg protein/min, whereas the rate of metab. was 37% higher with liver microsomes from mice.

Golam Shameem

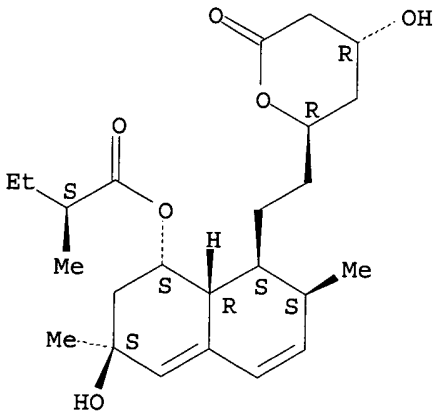
The profiles of metabolites were similar, but the relative abundance of individual metabolites was species dependent. Hydroxylation at the 6'-position was the principal pathway of lovastatin biotransformation, whereas hydroxylation at the 3''-position of the side chain was a minor pathway. In both species the 6'-.beta.-hydroxylovastatin accounted for half of the total metab. Liver microsomes from rats produced 2- to 4-fold higher amts. of the other 3 metabolites, namely, 6'-exomethylene-, 3''-hydroxy-, and the hydroxy acid form, than mouse liver microsomes. The conversion of lovastatin to the novel 6'-exomethylene metabolite was catalyzed by cytochrome P 450 since it required microsomes and NADPH and was inhibited by SKF-525A, metyrapone, and 2,4,-dichloro-6-phenylphenoxyethylamine (DPEA). Furthermore, neither 6'-.beta.-hydroxylovastatin nor the 6'-hydroxymethyl analogs could be demonstrated to be intermediates in the formation of the 6'-exomethylene metabolite. The hydroxy acid form of lovastatin was not a substrate for liver microsomes from either species.

IT **125638-71-3**
RL: FORM (Formation, nonpreparative)
(formation of, by liver microsomes, as lovastatin metabolite, cytochrome P 450 in)

RN 125638-71-3 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 54 OF 69 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1990:434323 CAPLUS

DOCUMENT NUMBER: 113:34323

TITLE: Biotransformation of lovastatin. I. Structure elucidation of in vitro and in vivo metabolites in the rat and mouse

AUTHOR(S): Vyas, Kamlesh P.; Kari, Prasad H.; Pitzenberger, Steven M.; Halpin, Rita A.; Ramjit, Harri G.; Arison, Byron; Murphy, Joan S.; Hoffman, William F.; Schwartz, Michael S.; et al.

CORPORATE SOURCE: Dep. Drug Metab., Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA

SOURCE: Drug Metab. Dispos. (1990), 18(2), 203-11
CODEN: DMDSAI; ISSN: 0090-9556

DOCUMENT TYPE: Journal

LANGUAGE: English

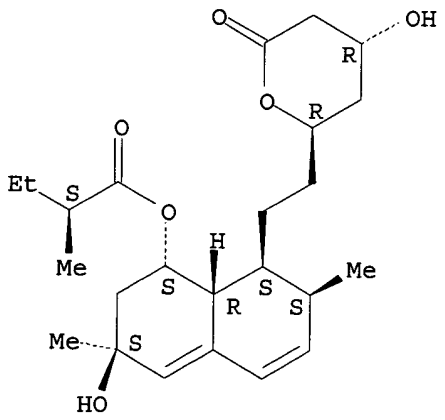
AB Structures of in vitro microsomal and in vivo metabolites of lovastatin, a new cholesterol-lowering drug, were elucidated with the combined application of HPLC, UV, fast atom bombardment-MS, and NMR spectroscopy. Liver microsomes from rats and mice catalyzed the biotransformation of lovastatin, primarily at the 6'-position of the mol., to form 6'-hydroxylovastatin and a novel 6'-exomethylene deriv. Hydroxylation at the 6'-position occurred stereoselectively, giving 6'-.beta.-hydroxylovastatin. Stereoselective hydroxylation at the 3''-position of the methylbutyryl side chain and hydrolysis of the lactone group to the corresponding hydroxy acid were the other two pathways of microsomal metab. 3'-Hydroxy-iso-.DELTA.-4',5'-lovastatin was isolated, but is not believed to be a direct metabolite since 6'-.beta.-hydroxylovastatin rearranges to this compd. under mildly acidic conditions. The major metabolites excreted in bile of rats treated with the hydroxy acid form of the drug wer identified as the 3'-hydroxy analog and a taurine conjugate of a .beta.-oxidn. product of lovastatin. The pentanoic acid deriv. of lovastatin, formed by .beta.-oxidn. of the heptanoic acid moiety, was a major metabolite in livers of mice dosed with the hydroxy acid form of lovastatin. The microsomal metabolites, in their hydroxy acid forms, were active inhibitors of HMG-CoA reductase. The relative enzyme inhibitory activities of hydroxy acid forms of lovastatin, 6'-.beta.-hydroxy-, 6'-exomethylene-, and 3''-hydroxylovastatin were 1, 0.6, 0.5, and 0.15, resp.

IT **125638-71-3**
RL: BIOL (Biological study)
(in liver, as lovastatin metabolite, structure of)

RN 125638-71-3 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 55 OF 69 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1990:171655 CAPLUS

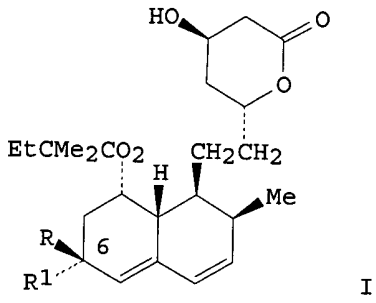
DOCUMENT NUMBER: 112:171655

TITLE: Regioselectivity and stereoselectivity in the metabolism of HMG-CoA reductase inhibitors

AUTHOR(S): Vyas, Kamlesh P.; Kari, Prasad H.; Pitzenberger, Steven M.

CORPORATE SOURCE: Dep. Drug Metab., Merck Sharp and Dohme Res. Lab.,

SOURCE: West Point, PA, 19486, USA
Biochem. Biophys. Res. Commun. (1990), 166(3), 1155-62
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

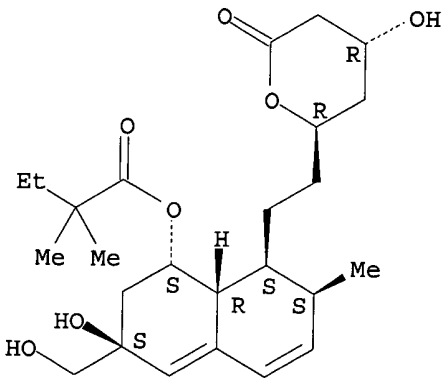
AB The biotransformation of 3 simvastatin analogs (I, R and R1 = H, CH2OH, Me) by rat liver microsomes was examd. These compds. differ from each other at the 6 position of the naphthalene ring. When 6-substituents were in the .alpha. configuration, rat liver microsomes catalyzed biotransformation primarily at the 6 position. Hydroxylation was stereoselective giving 6.beta.-hydroxy derivs. as major metabolites. In contrast, when the 6-substituent had a .beta.-configuration, metab. at this site was blocked. Rates of metab. (mols/mg protein/min) also indicated that 6.beta.-derivs. were poorer substrates than their 6.alpha.-counterparts. Thus, cytochrome P 450 exhibits a high degree of regio- and stereoselectivity in the metab. of HMG-CoA reductase inhibitors.

IT **126313-97-1**
RL: BIOL (Biological study)
(as simvastatin analog metabolite, in liver microsomes)

RN 126313-97-1 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-3-(hydroxymethyl)-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



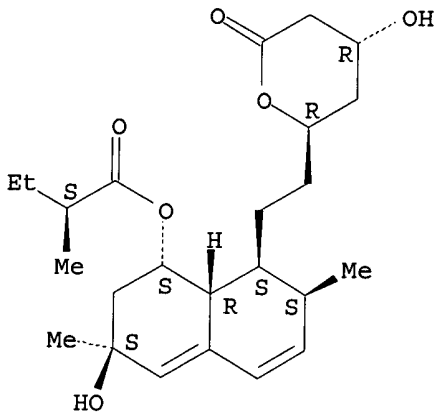
Golam Shameem

L7 ANSWER 56 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:111530 CAPLUS
DOCUMENT NUMBER: 112:111530
TITLE: Biotransformation of lovastatin. III. Effect of cimetidine and famotidine on in vitro metabolism of lovastatin by rat and human liver microsomes
AUTHOR(S): Vyas, Kamlesh P.; Kari, Prasad H.; Wang, Regina W.; Lu, Anthony Y. H.
CORPORATE SOURCE: Dep. Drug Metab., Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Biochem. Pharmacol. (1990), 39(1), 67-73
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of the H2-receptor antagonists, cimetidine and famotidine, on the microsomal metab. of [14C]lovastatin were investigated. Liver microsomes were prepd. from control, phenobarbital- and 3-methylcholanthrene-pretreated rats and humans (male and female). Concn.-dependent inhibition of the metab. of lovastatin (0.1 mM) was obsd. with cimetidine (0.1 to 1.0 mM). In contrast, famotidine at a similar concn. was a very weak inhibitor. The formation of 6'.beta.-hydroxy lovastatin, the major microsomal metabolite of lovastatin, was similarly inhibited. The results suggest that in vivo metabolic interaction with concomitantly administered lovastatin is less likely with famotidine than with cimetidine. Phenobarbital pretreatment produced 58% stimulation in overall metab., whereas 3-methylcholanthrene pretreatment had no effect relative to control rats (5.4 nmol/mg protein/min). Liver microsomes from phenobarbital-pretreated rats produced 67% more of the 6'.beta.-hydroxy lovastatin but 63-66% less of the 3''-hydroxy and 6'-exomethylene metabolites. Liver microsomes from 3-methylcholanthrene-treated rats also produced less 3''-hydroxy lovastatin (49%) but similar quantities of the other 2 metabolites. 6'.beta.-Hydroxy lovastatin was a major metabolite with human liver microsomes. Interestingly with these microsomes, hydroxylation at the 3''-position of the mol. was a negligible pathway and hydrolysis to the hydroxy acid form was not obsd. The formation of 6'-exomethylene lovastatin was also catalyzed by human liver microsomes (0.5 to 0.8 nmol/mg protein/min).

IT **125638-71-3**
RL: FORM (Formation, nonpreparative)
(formation of, as lovastatin metabolite, cimetidine and famotidine interaction with, in humans and lab. animals)
RN 125638-71-3 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

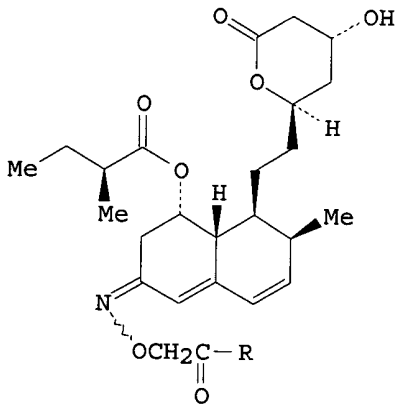
Absolute stereochemistry.



L7 ANSWER 57 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:55604 CAPLUS
DOCUMENT NUMBER: 112:55604
TITLE: Preparation of derivatives of pravastatin for inhibiting cholesterol biosynthesis
INVENTOR(S): DiPietro, Richard A.; Tu, Jan I; Turabi, Noor Z.
PATENT ASSIGNEE(S): Squibb, E. R., and Sons, Inc., USA
SOURCE: U.S., 8 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4857522	A	19890815	US 1988-171092	19880321
US 5047549	A	19910910	US 1989-338816	19890417
US 5155229	A	19921013	US 1991-724067	19910701

PRIORITY APPLN. INFO.: US 1988-171092 19880321
US 1989-338816 19890417
OTHER SOURCE(S): CASREACT 112:55604; MARPAT 112:55604
GI



I

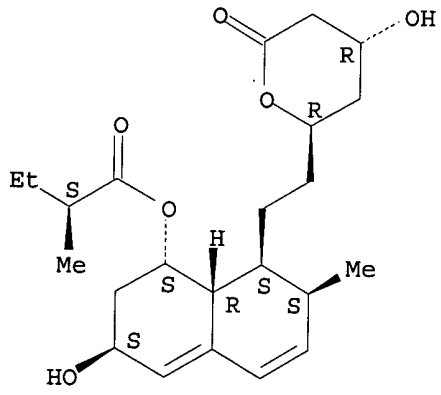
AB Pravastatin derivs. (I; R = OH, alkylamino, arylamino, heterocyclylamino) are prepd. which are useful in inhibiting cholesterol biosynthesis and in prepg. radiolabeled compds. for RIA of pravastatin and its derivs. (no data). Thus, pravastatin was lactonized, the 6-OH group was oxidized to a ketone and then converted to an oxime ester with HO2CCH2ONH2, and the product was amidated with histamine to yield I [R = [2-(1H-imdazolyl)ethyl]amino].

IT **85956-22-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, in hypolipemic pravastatin deriv. prepn.)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 58 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:48806 CAPLUS
DOCUMENT NUMBER: 112:48806
TITLE: Octahydronaphthalene oxime derivatives as cholesterol synthesis inhibitors, processes for their preparation, and compositions containing them
INVENTOR(S): Kurabayashi, Masaaki; Kogen, Hiroshi; Kadokawa,

Golam Shameem

Hiroshi; Kurihara, Hideshi; Hasegawa, Kazuo; Kuroda, Masao

PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 72 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 314435	A2	19890503	EP 1988-310026	19881025
EP 314435	A3	19900516		
EP 314435	B1	19930929		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
US 4997848	A	19910305	US 1988-261739	19881021
AT 95178	E	19931015	AT 1988-310026	19881025
ES 2011427	T3	19941116	ES 1988-310026	19881025
ZA 8808008	A	19900725	ZA 1988-8008	19881026
DK 8805993	A	19890428	DK 1988-5993	19881027
FI 8804968	A	19890428	FI 1988-4968	19881027
FI 91960	B	19940531		
FI 91960	C	19940912		
AU 8824397	A1	19890504	AU 1988-24397	19881027
AU 605925	B2	19910124		
JP 02000255	A2	19900105	JP 1988-270241	19881027
JP 2542429	B2	19961009		
CA 1336598	A1	19950808	CA 1988-581504	19881027
US 5403860	A	19950404	US 1990-627691	19901214
US 5658942	A	19970819	US 1995-399500	19950307

PRIORITY APPLN. INFO.:
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US 1988-261739 19881021
EP 1988-310026 19881025
US 1990-627691 19901214

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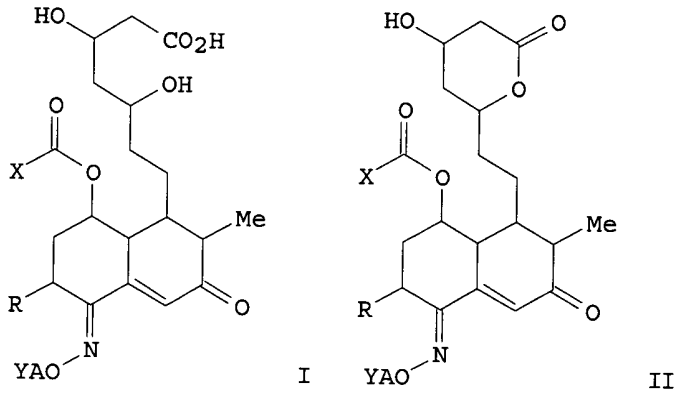


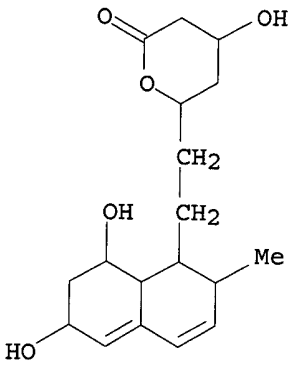
AB Octahydronaphthalene oxime derivs. I and II (R = H, Me, OH; X = alkyl, alkenyl, cycloalkyl, aryl, aralkyl, heterocyclo; A = single bond or alkylene, alkenylene, alkynylene, or alkadienylene; Y = H, aryl, cycloalkyl, heterocyclo) have antihypercholesteremic activity and may be used in the treatment of disorders arising from a blood cholesterol

imbalance in humans and other animals. They may be prepd. by introducing the group :NOAY in place of an O at the 4-position or introducing the group OCOX in place of a OH group at the 1-position in a corresponding compd. in which the OH at the 16-position is protected and deprotecting that group. Na 1-(2-methylbutyryl)-3,4-dihydro-6-oxo-4-benzyloxyiminoiso-ML-236A carboxylate (III) inhibited 3-hydroxy-3-methylglutaryl-CoA reductase with an IC50 of 18.5 nM. III was prepd. by reacting 16-tert-butyldimethylsiloxy-1-(2-methylbutyryl)-3,4-dihydro-4,6-dioxoiso-ML-236A lactone and O-benzylhydroxylamine hydrochloride, deprotecting, and treating with aq. NaOH.

IT **124807-74-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 124807-74-5 CAPLUS

CN 2H-Pyran-2-one, 6-[2-(1,2,6,7,8,8a-hexahydro-6,8-dihydroxy-2-methyl-1-naphthalenyl)ethyl]tetrahydro-4-hydroxy- (9CI) (CA INDEX NAME)



L7 ANSWER 59 OF 69 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1989:33265 CAPLUS

DOCUMENT NUMBER: 110:33265

TITLE: Metabolism of lovastatin by rat and human liver microsomes in vitro

AUTHOR(S): Greenspan, Michael D.; Yudkovitz, Joel B.; Alberts, Alfred W.; Argenbright, Lois S.; Arison, Byron H.; Smith, Jack L.

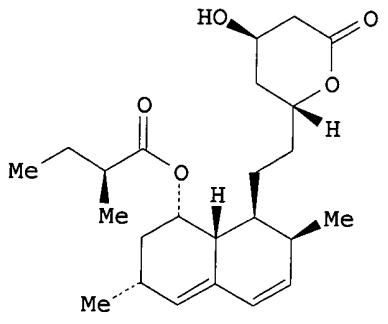
CORPORATE SOURCE: Merck Sharp and Dohme Res. Lab., Merck Inst. Ther. Res., Rahway, NJ, 07065-0900, USA

SOURCE: Drug Metab. Dispos. (1988), 16(5), 678-82
CODEN: DMDSAI; ISSN: 0090-9556

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



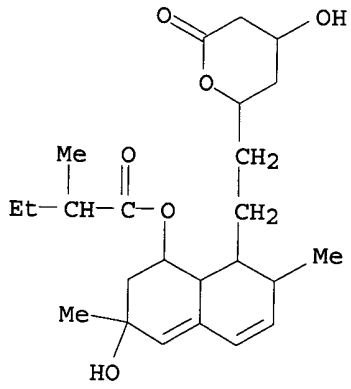
I

AB The metab. of lovastatin (Mevacor) (I) was examd. using isolated microsomes derived from the livers of normal and phenobarbital-treated rats and from human liver samples. Incubation of lovastatin with rat liver microsomes resulted in the formation of several polar metabolites of lovastatin. The metabolites were isolated by HPLC and identified by NMR and mass spectrometry. One fraction consisted of a 2:1 mixt. of 6-hydroxylovastatin and the rearrangement product .DELTA.4,5-3-hydroxylovastatin. Addn. of a trace of acid to this mixt. resulted in the formation of a single aromatized product, the desacyl-.DELTA.4a,6,8-dehydro analog of lovastatin. Another microsomal metabolite was detd. to be the .DELTA.4,8a,1-3-hydroxylovastatin deriv. The chromatog. pattern of metabolites produced from lovastatin by human liver microsomes was similar to that obtained with rat liver microsomes. Metab. of lovastatin by rat liver microsomes was both time and concn. dependent; optimal microsomal metab. occurred with 0.1 mM lovastatin, whereas higher lovastatin concns. inhibited the reaction. The open acid form of lovastatin was poorly metabolized by both the rat and the human liver microsomes.

IT **86330-87-2**
RL: BIOL (Biological study)
(as lovastatin metabolite, in liver microsomes of humans)

RN 86330-87-2 CAPLUS

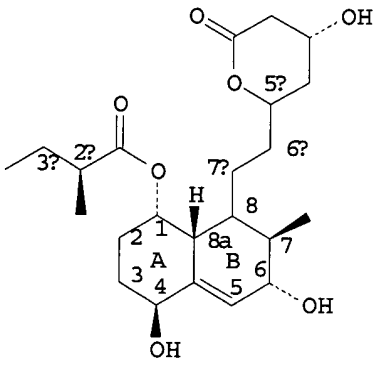
CN Butanoic acid, 2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)



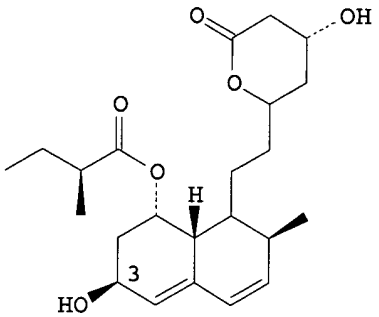
L7 ANSWER 60 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1988:5477 CAPLUS

Golam Shameem

DOCUMENT NUMBER: 108:5477
TITLE: A quantitative analysis of nuclear magnetic relaxation: the configuration and the conformation of ML-236B (mevastatin) metabolites
AUTHOR(S): Haruyama, Hideyuki; Kondo, Michio
CORPORATE SOURCE: Anal. Metab. Res. Lab., Sankyo Co. Ltd., Tokyo, 140, Japan
SOURCE: Chem. Pharm. Bull. (1987), 35(1), 170-81
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



II

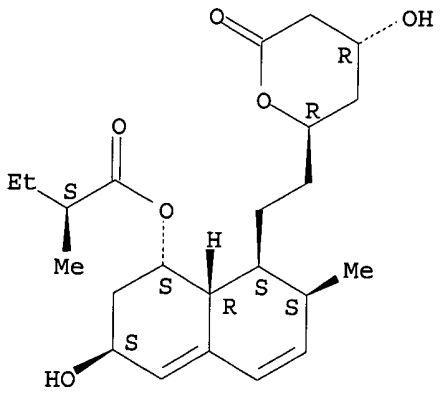
AB A quant. treatment of proton spin-lattice relaxation time (T1) and nuclear Overhauser effect (NOE) has been applied to the conformational anal. of two mevastatin metabolites I and II in soln. The T1 values and NOE factors predicted for several candidate conformers were compared with the obsd. ones. For I, the best agreements between obsd. and calcd. values were obtained when the A ring of its octalin moiety was assumed to adopt a chair conformation, and the B ring, a 7.beta.-sofa conformation. In addn. it was found that the .delta.-lactone side chain should be confined to some limited orientations to give calcd. values consistent with the obsd. T1 values and NOEs. Based on the x-ray derived geometry, a similar anal. was done for II, to check the validity of the method and to characterize the conformation of the .beta.-lactone side chain in soln. The .delta.-lactone side chain of I was concluded to have the same conformation as in the crystal state. The applicability of the distance geometry method to calc. the coordinates of small org. mols. was confirmed.

IT **85956-22-5**
RL: PRP (Properties)
(conformational anal. of)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



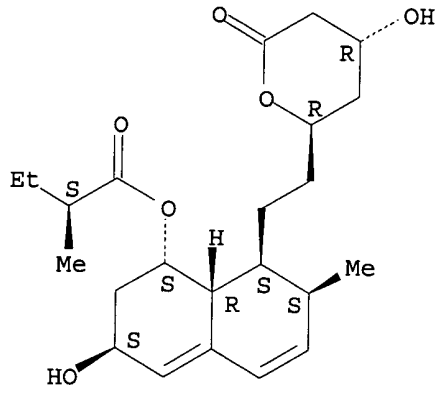
L7 ANSWER 61 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1986:625654 CAPLUS
DOCUMENT NUMBER: 105:225654
TITLE: Proton-NMR spectra of mono-hydroxy derivatives of ML-236B and MB-530B
AUTHOR(S): Kuwano, Harumitsu; Serizawa, Nobufusa; Hamano, Kiyoshi; Terahara, Akira
CORPORATE SOURCE: Anal. Metabol. Res. Lab., Sankyo Co., Ltd., Tokyo, 140, Japan
SOURCE: Sankyo Kenkyusho Nempo (1985), 37, 147-54
CODEN: SKKNAJ; ISSN: 0080-6064
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The 1H-NMR spectra of 5 microbial transformation products 3.beta.-hydroxy ML-236B, a 3.beta.-hydroxy ML-236B carboxylate (CS-514), 3.alpha.-hydroxy ML-236B, Na 6.alpha.-hydroxy iso-ML-236B carboxylate, and Na 6.alpha.-hydroxy iso-MB-530B carboxylate were measured at 400 MHz. Assignment of the 1H-NMR spectra was detd. by the doublet resonance method and stereostructural features of the mono-hydroxy derivs. discussed.

IT **85956-22-5 85956-23-6**
RL: PRP (Properties)
(NMR of protons in)

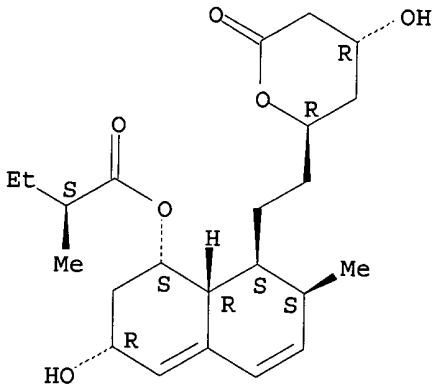
RN 85956-22-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

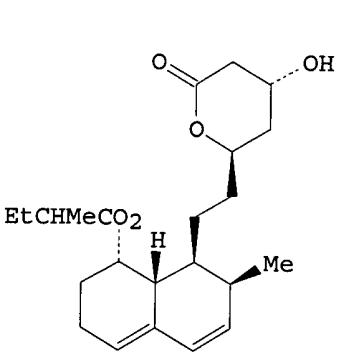


RN 85956-23-6 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 62 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:20934 CAPLUS
DOCUMENT NUMBER: 102:20934
TITLE: Microbial transformation of ML-236B (compactin) to M3, a mammalian metabolite of ML-236B
AUTHOR(S): Serizawa, Nobufusa; Nakagawa, Keiko; Tsujita, Yoshio; Terahara, Akira
CORPORATE SOURCE: Ferment. Res. Lab., Sankyo Co., Ltd., Tokyo, 140, Japan
SOURCE: Agric. Biol. Chem. (1984), 48(10), 2581-2
CODEN: ABCHA6; ISSN: 0002-1369
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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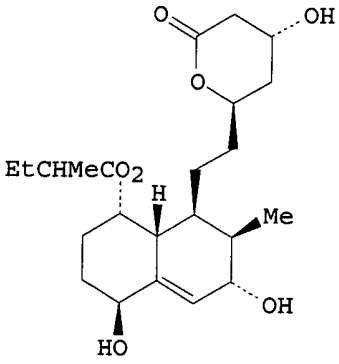


II

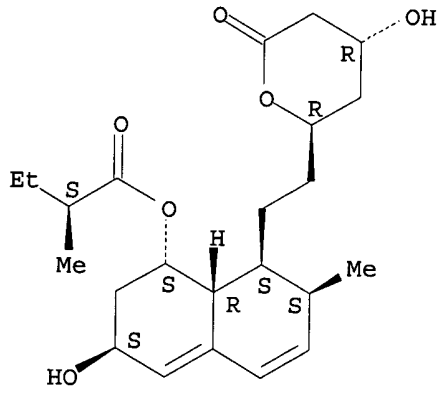
AB Nocardia autotrophica Subspecies amethystina was capable of hydroxylating ML-236B (I) to M3 (II). In addn., 3.alpha.- or 3.beta.-hydroxy-ML-236B and 6.alpha.-hydroxy-iso-ML-236B were found in the fermn.broth. The concn. of M3 in the lactone form for 50% inhibition of cholesterol formation was 65 ng/mL, as compared with 10 ng/mL in the case of ML-236B.

IT **85956-22-5 85956-23-6**
RL: FORM (Formation, nonpreparative)
(formation of, from ML-236B by Norcardia autotrophica)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

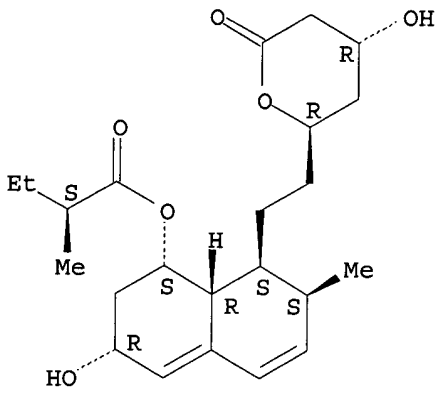
Absolute stereochemistry.



RN 85956-23-6 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

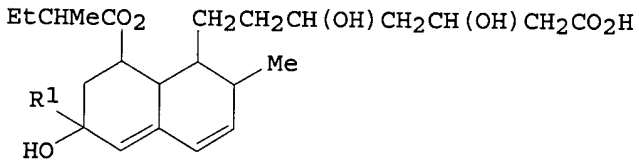
Absolute stereochemistry.



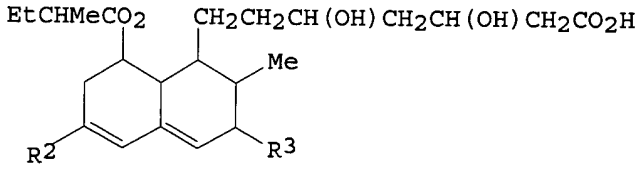
L7 ANSWER 63 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1984:428292 CAPLUS
DOCUMENT NUMBER: 101:28292
TITLE: Antihyperlipidemics
PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 14 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 59048418	A2	19840319	JP 1982-158605	19820910
JP 03037526	B4	19910605		

GI



I



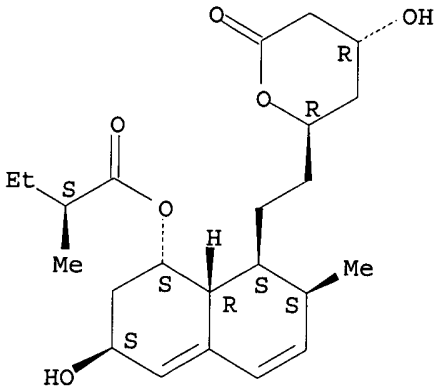
II

AB I or II (R1 and R2 = H or Me; R3 = OH or MeO), their salts, esters, and lactones, obtrained by extn. from Syncephalastrum nigricans or Absidia coerulea, are effective in controlling high serum levels of lipid peroxides. Capsules are prepd. contg. I (R1 = H) Na salt (II) [81131-70-6] 10, lactose 151.2, corn starch 37.8, and Mg stearate 1.0 part. II (25 mg/kg/day, orally for 5 wk) given to male dogs decreased serum lipid peroxide levels about 30%.

Golam Shameem

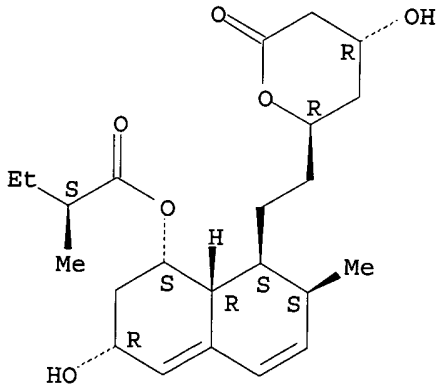
IT **85956-22-5**
RL: BIOL (Biological study)
(of Absidia coerulea, as antihyperlipemic)
RN 85956-22-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **85956-23-6**
RL: BIOL (Biological study)
(of Syncephalastrum nigricans, as antihyperlipemic)
RN 85956-23-6 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



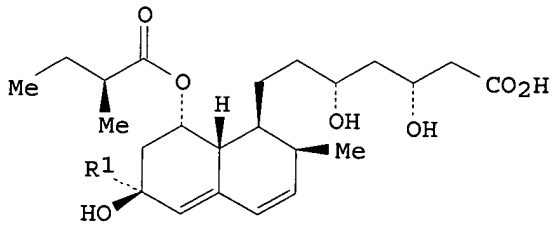
L7 ANSWER 64 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1984:96708 CAPLUS
DOCUMENT NUMBER: 100:96708
TITLE: Therapeutic agents for treatment of ischemic cardiopathy
PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 14 pp.

Golam Shameem

CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 58109416	A2	19830629	JP 1981-206595	19811221
JP 01045448	B4	19891003		

GI



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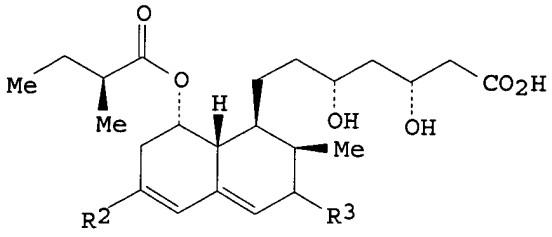


II

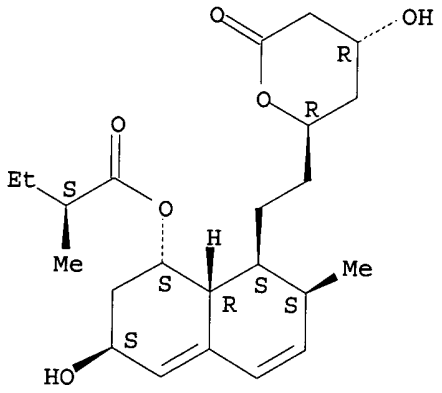
AB The carboxylic acids I and II (R1 and R2 = H or Me; R3 = OH or OMe), their salts, esters, and lactones are effective in treatment of ischemic cardiopathy. Thus, III (I-Na; R1 = H) (20 mg/kg/day, orally for 4 wk) given to dogs maintained normal elec. activities in the heart even after crit. stenosis was induced exptl. in the coronary artery.

IT **85956-22-5 85956-23-6**
RL: BIOL (Biological study)
(heart ischemia treatment with)

RN 85956-22-5 CAPLUS

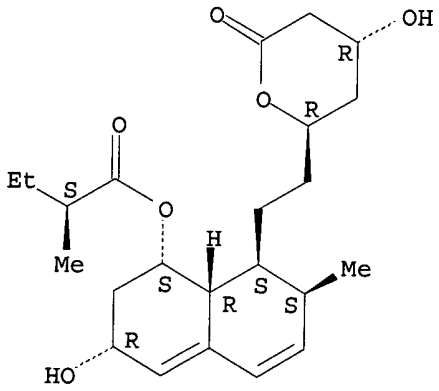
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 85956-23-6 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

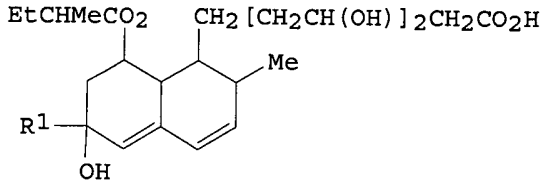
Absolute stereochemistry.



L7 ANSWER 65 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1983:516076 CAPLUS
DOCUMENT NUMBER: 99:116076
TITLE: Synergistic antichloesteremic activity of ML-236B derivatives
PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 16 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 58090509	A2	19830530	JP 1981-188530	19811125
JP 01005571	B4	19890131		

GI



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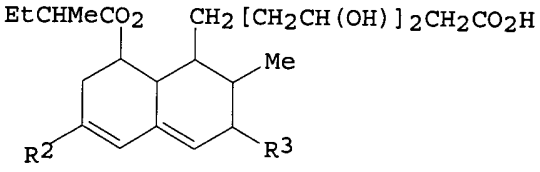

II

AB The carboxylic acids I or II (R1 and R2 = H or Me; R3 = H or OMe) (its salts, esters, and lactones) in combination with basic anion-exchange resins, which bind to bile acids, are synergistic anticholestermics. Thus, 20 mg III Na salt [87098-76-8]/kg/day or 1 g cholestyramine [11041-12-6] given orally to dogs decreased blood cholesterol 35 and 33%, resp., but the combined administration decreased it 76% in 4 wk.

IT **85956-23-6**
RL: PROC (Process)
(isolation of, as anticholestermic from Syncephalastrum nigricans)

RN 85956-23-6 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

*** SUBSTANCE INFORMATION NOT AVAILABLE ***

L7 ANSWER 66 OF 69 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1983:468799 CAPLUS
DOCUMENT NUMBER: 99:68799
TITLE: 3-Hydroxy-ML-236b derivatives known as M-4 and M-4'
PATENT ASSIGNEE(S): Sankyo Co., Ltd. , Japan
SOURCE: Belg., 33 pp.
CODEN: BEXXAL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
BE 895080	A1	19830316	BE 1982-209527	19821119
JP 58089191	A2	19830527	JP 1981-186641	19811120
JP 03071116	B4	19911112		
AU 8290610	A1	19830526	AU 1982-90610	19821116
AU 551720	B2	19860508		
CA 1186647	A1	19850507	CA 1982-415650	19821116
SE 8206580	A	19830521	SE 1982-6580	19821118
SE 453996	B	19880321		
SE 453996	C	19880630		
US 4537859	A	19850827	US 1982-442840	19821118
DK 8205161	A	19830521	DK 1982-5161	19821119
DK 159328	B	19901001		
DK 159328	C	19910225		

FI 8203978	A	19830521	FI 1982-3978	19821119
FI 70925	B	19860718		
FI 70925	C	19861027		
FR 2516935	A1	19830527	FR 1982-19433	19821119
FR 2516935	B1	19850208		
DE 3242849	A1	19830601	DE 1982-3242849	19821119
DE 3242849	C2	19890105		
NL 8204505	A	19830616	NL 1982-4505	19821119
NL 194373	B	20011001		
ZA 8208535	A	19831026	ZA 1982-8535	19821119
ES 517542	A1	19840116	ES 1982-517542	19821119
CH 651065	A	19850830	CH 1982-6754	19821119
GB 2111052	A1	19830629	GB 1982-33267	19821122
GB 2111052	B2	19850509		
AT 8204251	A	19880715	AT 1982-4251	19821122
AT 387585	B	19890210		

PRIORITY APPLN. INFO.: JP 1981-186641 A 19811120

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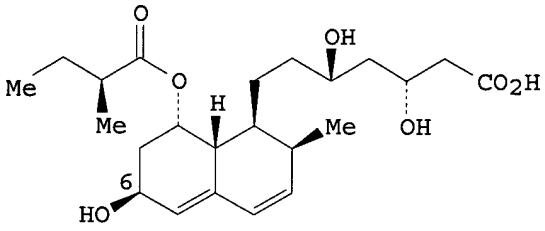


I

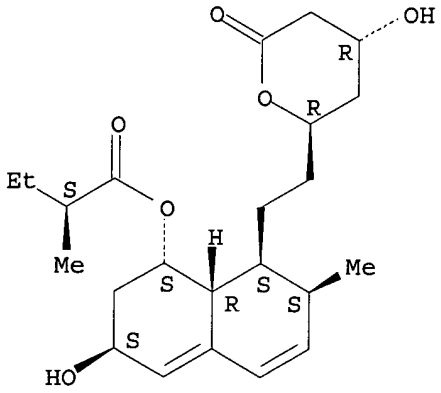
AB Compds. M-4 (I) and M-4' (II-6-epi-I) are produced by hydroxylation of ML-236b (III-6-deoxy-I) with Nocardia. Thus, N. autotrophica canberrica FERM P-6182 was inoculated into 2 L pH 7.0 medium contg. glycerol 0.5, sucrose 2, soybean meal 1, yeast 1, corn steep liquor 0.5, and NaCl 0.001% and incubated at 26.degree. for 2 days with shaking. Then 0.5% III was added and incubation was continued for 5 days. The broth was filtered and the filtrate made pH 3.0 and extd. with EtOAc. I and II could not be sepd. by chromatog. The ext. was dried and treated with diazomethane to yield 180 mg Me M-4 carboxylate [81131-72-8] and 110 mg Me M-4' carboxylate [81131-75-1], which were sepd. by chromatog. on silica gel.

IT **85956-22-5P 85956-23-6P**
RL: BMF (Bioindustrial manufacture); BIOL (Biological study); PREP (Preparation)
(manuf. of, with Nocardia)

RN 85956-22-5 CAPLUS

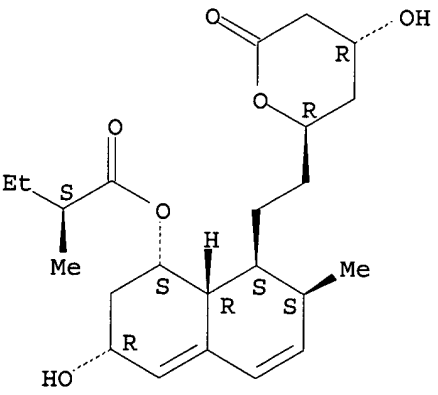
CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

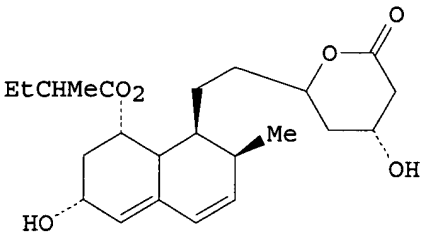


RN 85956-23-6 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

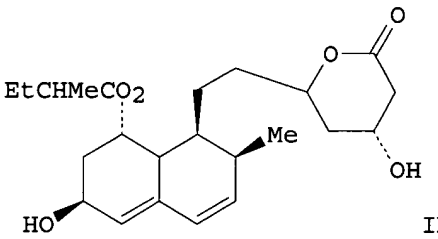
Absolute stereochemistry.



L7 ANSWER 67 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1983:435806 CAPLUS
DOCUMENT NUMBER: 99:35806
TITLE: 3.alpha.-Hydroxy-ML-236B (3.alpha.-hydroxycompactin), microbial transformation product of ML-236B (compactin)
AUTHOR(S): Serizawa, Nobufusa; Nakagawa, Keiko; Tsujita, Yoshio; Terahara, Akira; Kuwano, Harumitsu
CORPORATE SOURCE: Ferment. Res. Lab., Sankyo Co., Ltd., Tokyo, 140, Japan
SOURCE: J. Antibiot. (1983), 36(5), 608-10
CODEN: JANTAJ; ISSN: 0021-8820
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



II

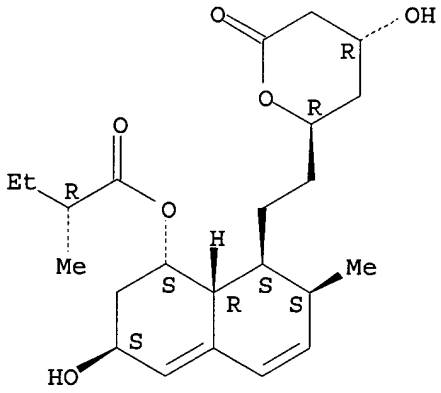
AB Various strains of Syncephalastrum nigricans, S. racemosum, and Mucor hiemalis hydroxylated compactin (I). S. nigricans SANK 42372 achieved 26% conversion of I to the 3.alpha.-hydroxy deriv. (II). M. hiemalis SANK 36372 achieved 72% conversion of I to the 3.beta.-hydroxy deriv. II was a better inhibitor of in vitro cholesterol formation than was its stereoisomer.

IT **81093-38-1P 81131-76-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, by microbial transformation)

RN 81093-38-1 CAPLUS

CN Butanoic acid, 2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

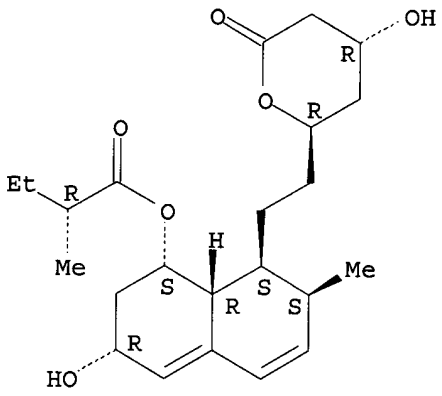
Absolute stereochemistry.



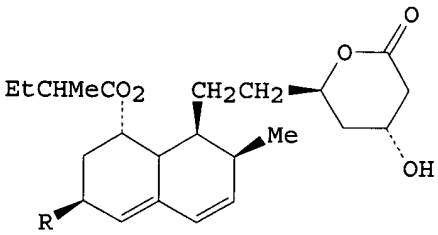
RN 81131-76-2 CAPLUS

CN Butanoic acid, 2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.alpha.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 68 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1983:435805 CAPLUS
DOCUMENT NUMBER: 99:35805
TITLE: Microbial hydroxylation of ML-236B (compactin) and monacolin K (MB-530B)
AUTHOR(S): Serizawa, Nobufusa; Nakagawa, Keiko; Hamano, Kiyoshi; Tsujita, Yoshio; Terahara, Akira; Kuwano, Harumitsu
CORPORATE SOURCE: Ferment. Res. Lab., Sankyo Co., Ltd., Tokyo, 140, Japan
SOURCE: J. Antibiot. (1983), 36(5), 604-7
CODEN: JANTAJ; ISSN: 0021-8820
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



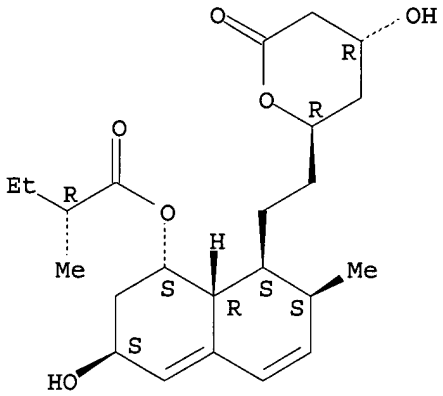
I, R=H
II, R=Me

AB Hydroxylation of ML-236B (I) and MB-530B (II) was carried out utilizing Mucor hiemalis. The products were hydroxylated in the 3 or 6 position. Tests to det. the inhibitory activity of these compds. against cholesterol synthesis in vitro showed that addn. of the hydroxyl group in the 3 position confered 2-3-fold enhancement of their activity.

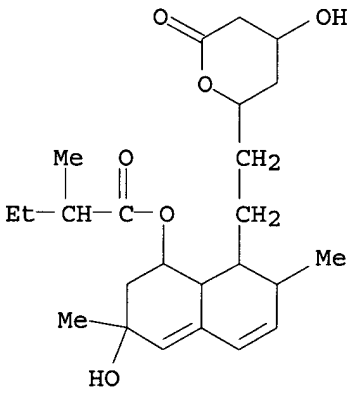
IT **81093-38-1 86330-87-2**
RL: FORM (Formation, nonpreparative)
(formation of, by Mucor, and cholesterol formation inhibition by)

RN 81093-38-1 CAPLUS
CN Butanoic acid, 2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.(S*),3.beta.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 86330-87-2 CAPLUS
CN Butanoic acid, 2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)



L7 ANSWER 69 OF 69 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1982:404664 CAPLUS
DOCUMENT NUMBER: 97:4664
TITLE: ML-236B derivatives and their pharmaceutical use
INVENTOR(S): Terahara, Akira; Tanaka, Minoru
PATENT ASSIGNEE(S): Sankyo Co., Ltd. , Japan
SOURCE: Ger. Offen., 73 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3122499	A1	19811224	DE 1981-3122499	19810605
DE 3122499	C2	19871126		
JP 57002240	A2	19820107	JP 1980-76127	19800606
JP 61013699	B4	19860415		

Golam Shameem

JP 57108039	A2	19820705	JP 1980-115483	19800822
JP 63048858	B4	19880930		
JP 57050894	A2	19820325	JP 1980-124385	19800908
JP 62054476	B4	19871116		
JP 57067575	A2	19820424	JP 1980-130311	19800919
JP 63021672	B4	19880509		
DK 8102470	A	19811207	DK 1981-2470	19810604
DK 149080	B	19860113		
DK 149080	C	19860728		
FI 8101762	A	19811207	FI 1981-1762	19810605
FI 71168	B	19860814		
FI 71168	C	19861124		
SE 8103560	A	19811207	SE 1981-3560	19810605
SE 453389	B	19880201		
SE 453389	C	19880519		
AU 8171376	A1	19811210	AU 1981-71376	19810605
AU 549988	B2	19860227		
FR 2483912	A1	19811211	FR 1981-11190	19810605
FR 2483912	B1	19850712		
NL 8102737	A	19820104	NL 1981-2737	19810605
NL 191738	B	19960102		
NL 191738	C	19960503		
US 4346227	A	19820824	US 1981-270846	19810605
ES 502827	A1	19821101	ES 1981-502827	19810605
CH 655090	A	19860327	CH 1981-3722	19810605
GB 2077264	A	19811216	GB 1981-17450	19810608
GB 2077264	B2	19840426		
CA 1150170	A1	19830719	CA 1981-379232	19810608
BE 889150	A1	19811209	BE 1981-205046	19810609
AT 8102567	A	19830915	AT 1981-2567	19810609
AT 374495	B	19840425		
US 4410629	A	19831018	US 1982-351974	19820224
US 4448979	A	19840515	US 1982-351975	19820224

PRIORITY APPLN. INFO.:

JP 1980-76127 19800606
JP 1980-115483 19800822
JP 1980-124385 19800908
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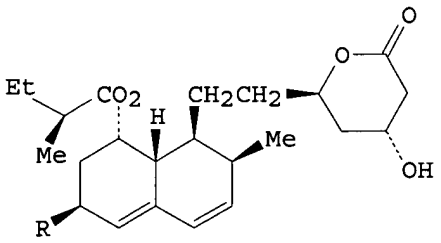
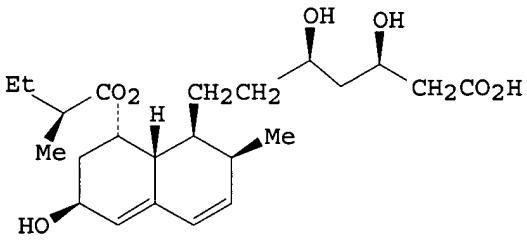


I, R=H
III, R=OH



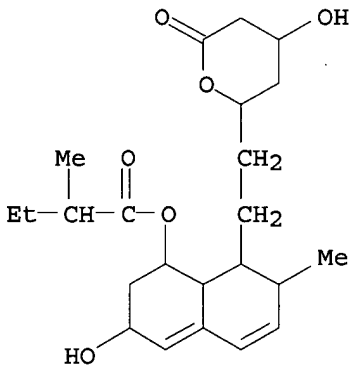
II

AB cholesterol [57-88-5] Formation inhibitors are produced from ML 236B (I) [58948-09-7] by fermn. with fungi or bacteria. Thus, spores of Absidia coerulea IFO 4423 were inoculated into a pH 7 medium contg. glucose 2, K2HPO4 0.15, MgSO4.7H2O 0.15, NH4NO3 0.1, peptone 0.1, corn steep liquor 0.2, yeast ext. 0.1, and ZnSO4.7H2O 0.001% at 26.degree. for 2 days with shaking. Then, 0.05% I Na salt was added and incubation was continued for 5 days. The broth filtrate was made pH 3 with TCA and extd. with EtOAc. The ext. was chromatographed on silica gel to sep. M-4 (II) [81093-37-0]. M-4 was lactonized with a catalytic amt. of TCA to form 50.1 mg M-4 lactone (III) [60478-65-1].

IT **81131-71-7P 81131-76-2P**
RL: BMF (Bioindustrial manufacture); BIOL (Biological study); PREP (Preparation)
(manuf. of, from substance ML236B by fermn.)

RN 81131-71-7 CAPLUS

CN Butanoic acid, 2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

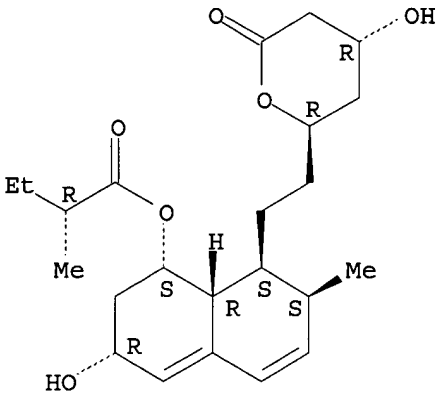


RN 81131-76-2 CAPLUS

CN Butanoic acid, 2-methyl-, 1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester,

[1S-[1.alpha.(S*),3.alpha.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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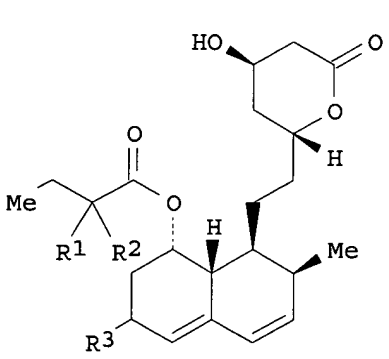
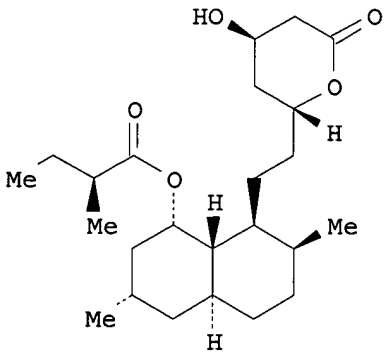
L8 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:2410 CAPLUS
DOCUMENT NUMBER: 134:193253
TITLE: Oxidation of HMG-CoA reductase inhibitors by tert-butoxyl and 1,1-diphenyl-2-picrylhydrazyl radicals: model reactions for predicting oxidatively sensitive compounds during preformulation
AUTHOR(S): Karki, Shyam B.; Treemaneekarn, Varaporn; Kaufman, Michael J.
CORPORATE SOURCE: Pharmaceutical Research and Development Department, Merck Research Laboratories, West Point, PA, 19486, USA
SOURCE: J. Pharm. Sci. (2000), 89(12), 1518-1524
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



II

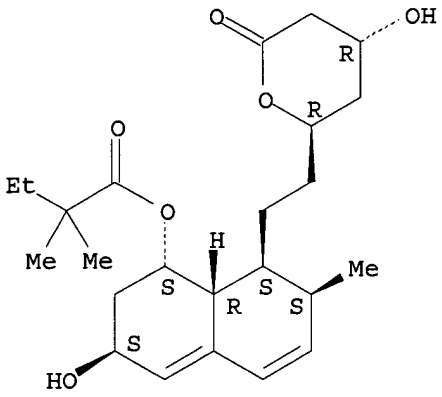
AB Hydrogen atom abstraction rate consts. for the reaction of tert-butoxyl and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical with the HMG-CoA reductase inhibitors lovastatin (I, R1 = H, R2 = .beta.-Me, R3 = .alpha.-Me), simvastatin (I, R1 = Me, R2 = Me, R3 = .alpha.-Me), and statins I (I, R1 = H, R2 = .beta.-Me, R3 = H), II (I, R1 = H, R2 = .beta.-Me, R3 = .beta.-CH2OH), III (II), and IV (I, R1 = Me, R2 = Me, R3 = .beta.-OH) were measured. This series of diene-contg. drugs is known to be prone to oxidn. The tert-butoxyl radical was generated by the thermolysis of di-tert-butylperoxyoxalate at 40.degree.C. A competitive kinetic method was used to det. the relative rate of hydrogen atom abstraction by tert-butoxyl radical to .beta.-scission. The abs. rate consts. were calcd. using the exptl. detd. product ratios of t-butanol to acetone and the known rate of .beta.-scission of tert-butoxyl radical. The rate consts. for the reaction with DPPH radical were measured spectrophotometrically by monitoring the loss of DPPH radical as a function of substrate concn. The rate consts. correlate well with the structure of the mols. studied. These kinetic techniques allow for oxidatively sensitive compds. to be identified early in the drug development cycle. The tert-butoxyl radical, a strong hydrogen atom abstractor, is representative of the hydroxyl (.cntdot.OH) and alkoxyl (.cntdot.OR) radicals; in contrast the DPPH radical, a much weaker radical, is a good kinetic model for hydroperoxyl (.cntdot.OOH) and peroxyl (.cntdot.OOR) radicals. These kinetic methods can be used to quant. assess the lability of drug candidates towards reaction with oxygen-centered radicals at an early stage of development and facilitate the design of inhibiting strategies.

IT **327037-01-4**, Statin IV
RL: PEP (Physical, engineering or chemical process); PRP (Properties); RCT (Reactant); **PROC (Process)**
(oxidn. of HMG-CoA reductase inhibitors by tert-butoxyl and 1,1-diphenyl-2-picrylhydrazyl radicals)

RN 327037-01-4 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16
REFERENCE(S):
(1) Bartlett, P; J Am Chem Soc 1960, V82, P1762 CAPLUS
(3) Cuthbertson, M; Aust J Chem 1983, V36, P1957 CAPLUS
(4) Ellison, D; Analytical profiles of drug substances and excipients 1993, V22, P359 CAPLUS
(5) Kaufman, M; Pharm Res 1990, V7, P289 CAPLUS
(6) Kennedy, B; Can J Chem 1966, V44, P2381 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:165425 CAPLUS
DOCUMENT NUMBER: 133:53181
TITLE: Effect of multiple cilostazol doses on single-dose lovastatin pharmacokinetics in healthy volunteers
AUTHOR(S): Bramer, Steven L.; Brisson, Jerry; Corey, Alfred E.; Mallikaarjun, Suresh
CORPORATE SOURCE: Otsuka America Pharmaceutical, Inc., Rockville, MD, USA
SOURCE: Clin. Pharmacokinet. (1999), 37(Suppl. 2), 69-77
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Volunteers received single oral doses of 80 mg lovastatin on days 1, 7 and 9, as well as 100 mg oral cilostazol twice daily on days 2-8, followed by a single oral 150-mg cilostazol dose on day 9. Pharmacokinetic parameters were calcd. by using plasma concns. of lovastatin and its .beta.-hydroxy metabolite and of cilostazol and its metabolites. Differences in the pharmacokinetics of each drug when given alone or in combination were assessed by anal. of variance. The max. obsd. plasma concn. (Cmax) of lovastatin or its metabolite did not differ significantly when lovastatin was given alone and when it was given with 100 mg cilostazol. The mean ratios of the area under the plasma concn.-time curve from zero to the time of the last measurable concn. (AUCt) for lovastatin coadministered with 100 mg cilostazol to that with lovastatin given alone were 1.6 for lovastatin and 1.7 for its metabolite. With 150 mg cilostazol, lovastatin Cmax did not change, whereas Cmax of the metabolite increased 2.2-fold. The mean AUCt ratios for lovastatin given with 150 mg cilostazol/lovastatin given alone were 1.6 and 2.0 for lovastatin and its metabolite, resp. All the increases in lovastatin and metabolite AUC were significant, except for the 1.6-fold increase in lovastatin AUC with 150 mg cilostazol. Maximum steady-state plasma drug concn. and AUC during a

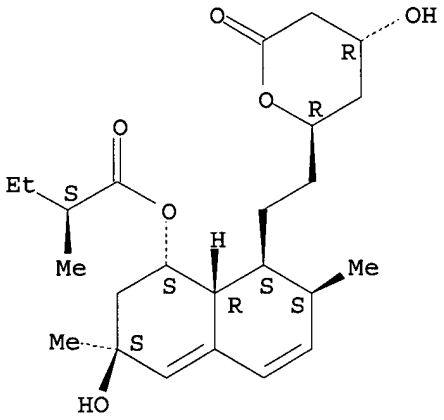
dosage (AUCt) of 100 mg cilostazol twice daily decreased 14 and 15%, resp., upon lovastatin coadministration. Thus, exposure to lovastatin and its metabolite is increased by only .ltoreq.2-fold when cilostazol is coadministered, which is considerably less than that obsd. for potent cytochrome P 450 3A inhibitors such as itraconazole and grapefruit juice. Absorption of cilostazol decreased approx. 15% when it was given with lovastatin. No dosage adjustments are necessary for cilostazol when coadministered with lovastatin, whereas lovastatin dose redns. may be needed when the 2 drugs are given together.

IT **125638-71-3**
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); **PROC (Process)**
(multiple cilostazol doses effect on single-dose lovastatin pharmacokinetics in humans in relation to formation of)

RN 125638-71-3 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 8
REFERENCE(S):
(1) Abbas, R; To be published in Hum Exp Toxicol
(2) Jusko, W; Applied pharmacokinetics -- principles of therapeutic drug monitoring 1986
(3) Kantola, T; Clin Pharmacol Ther 1998, V63(4), P397 CAPLUS
(6) Neuvonen, P; Clin Pharmacol Ther 1996, V60(1), P54 CAPLUS
(8) Transon, C; Eur J Clin Pharmacol 1996, V50(3), P209 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:632712 CAPLUS
DOCUMENT NUMBER: 132:93
TITLE: Small intestinal metabolism of the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor lovastatin and comparison with pravastatin
AUTHOR(S): Jacobsen, Wolfgang; Kirchner, Gabriele; Hallensleben, Katrin; Mancinelli, Laviero; Deters, Michael; Hackbarth, Ingelore; Baner, Karen; Benet, Leslie Z.; Sewing, Karl-Friedrich; Christians, Uwe

Golam Shameem

CORPORATE SOURCE: Department of Biopharmaceutical Sciences, School of Pharmacy, University of California, San Francisco, CA, USA
SOURCE: J. Pharmacol. Exp. Ther. (1999), 291(1), 131-139
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

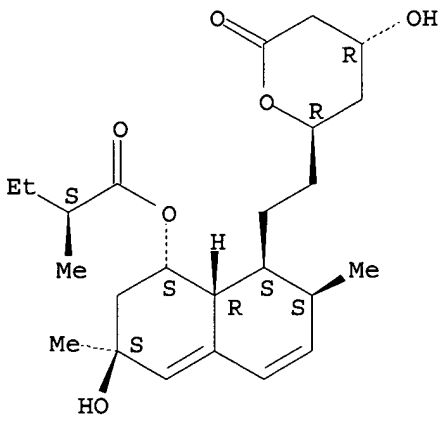
AB We compared the intestinal metab. of the structurally related 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors lovastatin and pravastatin in vitro. Human small intestinal microsomes metabolized lovastatin to its major metabolites 6'.beta.-hydroxy (apparent Km = 11.2.+-.3.3 .mu.M) and 6'-exomethylene (apparent Km = 22.7.+-.9.0 .mu.M) lovastatin. The apparent Km values were similar for lovastatin metab. by human liver microsomes. 6'.beta.-Hydroxylovastatin formation by pig small intestinal microsomes was inhibited with the following inhibition Ki values: cyclosporine, 3.3.+-.1.2 .mu.M; ketoconazole, 0.4.+-.0.1 .mu.M; and troleandomycin, 0.8.+-.0.9 .mu.M. Ki values for 6'-exomethylene lovastatin were similar. Incubation of pravastatin with human small intestinal microsomes resulted in the generation of 3'.alpha.,5'.beta.,6'.beta.-trihydroxypravastatin (apparent Km = 4560.+-.1410 .mu.M) and hydroxypravastatin (apparent Km = 5290.+-.1740 .mu.M). In addn., as in the liver, pravastatin was metabolized in the small intestine by sulfation and subsequent degrdn. to its main metabolite 3'.alpha.-iso-pravastatin. It was concluded that lovastatin is metabolized by cytochrome P 450 3A enzymes in the small intestine. Compared with lovastatin, the cytochrome P 450-dependent intestinal intrinsic clearance of pravastatin was >5000-fold lower and cannot be expected to significantly affect its oral bioavailability or to be a significant site of drug interactions.

IT **125638-71-3**, 6'.beta.-Hydroxylovastatin
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); **PROC (Process)**
(small intestinal metab. of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor lovastatin and comparison with pravastatin)

RN 125638-71-3 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



Golam Shameem

REFERENCE COUNT: 39
REFERENCE(S):
(1) Benet, L; J Control Rel 1996, V39, P139 CAPLUS
(3) Dimitroulakos, J; Nat Med 1996, V2, P326 CAPLUS
(4) Estabrook, R; Methods Enzymol 1978, V52, P212 CAPLUS
(5) Everett, D; Drug Metab Dispos 1991, V19, P740 CAPLUS
(6) Flint, O; Toxicol Appl Pharmacol 1997, V145, P99 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:587216 CAPLUS
DOCUMENT NUMBER: 131:346095
TITLE: Grapefruit juice increases serum concentrations of atorvastatin and has no effect on pravastatin
AUTHOR(S): Lilja, Jari J.; Kivisto, Kari T.; Neuvonen, Pertti J.
CORPORATE SOURCE: Department of Clinical Pharmacology, University of Helsinki and Helsinki University Central Hospital, Helsinki, FIN-00290, Finland
SOURCE: Clin. Pharmacol. Ther. (St. Louis) (1999), 66(2), 118-127
CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: Grapefruit juice greatly increases the bioavailability of lovastatin and simvastatin. We studied the effect of grapefruit juice on the pharmacokinetics of atorvastatin and pravastatin. Methods: Two randomized, two-phase crossover studies were performed; study I with atorvastatin in 12 healthy volunteers and study II with pravastatin in 11 healthy volunteers. In both studies, volunteers took 200 mL double-strength grapefruit juice or water three times a day for 2 days. On day 3, each subject ingested a single 40 mg dose of atorvastatin (study I) or pravastatin (study II) with either 200 mL grape-fruit juice or water, and an addnl. 200 mL was ingested 1/2 h and 1 1/2 h later. In addn., subjects took 200 mL grapefruit juice or water three times a day on days 4 and 5 in study I. In study I, serum concns. of atorvastatin acid, atorvastatin lactone, 2-hydroxyatorvastatin acid, 2-hydroxyatorvastatin lactone, and active and total 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitors were measured up to 72 h. In study II, pravastatin, pravastatin lactone, and active and total HMG-CoA reductase inhibitors were measured up to 24 h. Results: Grapefruit juice increased the area under the serum concn.-time curve of atorvastatin acid from time zero to 72 h [AUC(0-72)] 2.5-fold (P <.01), whereas the peak serum concn. (Cmax) was not significantly changed. The time of the peak concn. (tmax) and the elimination half-life (t1/2) of atorvastatin acid were increased (P <.01). The AUC(0-72) of atorvastatin lactone was increased 3.3-fold (P <.01) and the Cmax 2.6-fold (P <.01) by grapefruit juice, and the tmax and t1/2 were also increased (P <.05). Grapefruit juice decreased the Cmax (P <.001) and AUC(0-72) (P <.001) of 2-hydroxyatorvastatin acid and increased its tmax and t1/2 (P <.01). Grapefruit juice also decreased the Cmax (P <.001) and AUC(0-72) (P <.05) of 2-hydroxyatorvastatin lactone. The AUC(0-72) values of active and total HMG-CoA reductase inhibitors were increased 1.3-fold (P <.05) and 1.5-fold (P <.01), resp., by grapefruit juice. In study II, the only significant change obsd. in the pharmacokinetics of pravastatin was prolongation of the tmax of active HMG-CoA reductase inhibitors by grapefruit juice (P <.05). Conclusions: Grapefruit juice significantly increased serum concns. of atorvastatin acid, atorvastatin lactone, and active and total HMG-CoA reductase

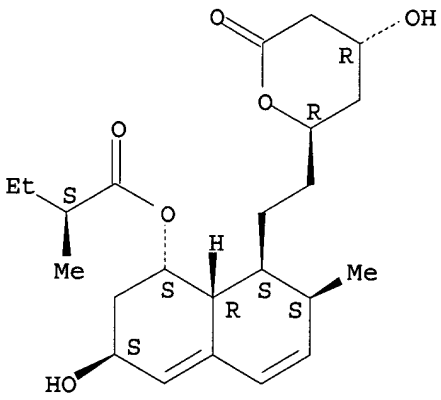
inhibitors, probably by decreasing CYP3A4-mediated first-pass metab. of atorvastatin in the small intestine. On the other hand, grapefruit juice had no effect on the pharmacokinetics of pravastatin. Concomitant use of atorvastatin and at least large amts. of grapefruit juice should be avoided, or the dose of atorvastatin should be reduced accordingly.

IT **85956-22-5**, Pravastatin lactone
RL: BPR (Biological process); BIOL (Biological study); **PROC (Process)**
(grapefruit juice increases serum concns. of atorvastatin and has no effect on pravastatin)

RN 85956-22-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3S,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 24
REFERENCE(S):
(2) Bailey, D; Br J Clin Pharmacol 1995, V40, P135 CAPLUS
(3) Bailey, D; Clin Pharmacol Ther 1993, V54, P589 CAPLUS
(4) Bailey, D; Clin Pharmacol Ther 1993, V53, P637 CAPLUS
(7) Haria, M; Drugs 1997, V53, P299 CAPLUS
(9) Jacobsen, W; Drug Metab Dispos 1999, V27, P173 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:316101 CAPLUS
DOCUMENT NUMBER: 122:263678
TITLE: Synthesis of hydroxymethylglutaryl-CoA reductase inhibitors
INVENTOR(S): Carta, Giorgio; Conder, Michael J.; Gainer, John Lloyd; Stieberg, Robert W.; Vinci, Victor A.; Weber, Timothy Wallace
PATENT ASSIGNEE(S): Merck and Co., Inc., USA; University of Virginia Alumni Patents Foundation
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

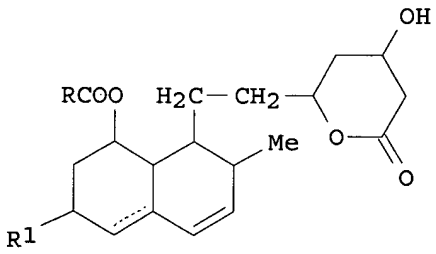
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9426920	A1	19941124	WO 1994-US5019	19940506
W: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TT, UA, US, UZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5420024	A	19950530	US 1993-60847	19930511
CA 2161788	AA	19941124	CA 1994-2161788	19940506
AU 9469072	A1	19941212	AU 1994-69072	19940506
AU 673268	B2	19961031		
EP 698111	A1	19960228	EP 1994-917312	19940506
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 08510128	T2	19961029	JP 1994-525564	19940506

PRIORITY APPLN. INFO.: US 1993-60847 19930511
WO 1994-US5019 19940506

OTHER SOURCE(S): MARPAT 122:263678

GI



I R = alkyl; R^1 = H, alkyl

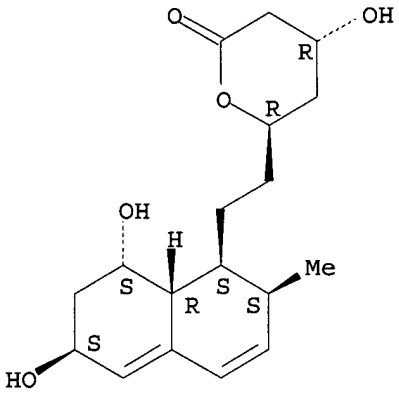
AB HMG-CoA reductase inhibitors of formula (I) are formed by esterification employing an immobilized lipase in a nonaq. org. solvent. Thus, lovastatin diol lactone was incubated with nylon-immobilized lipase type VII from Candida cylindracea and 2-methylbutyric acid in a solvent of 1:1 CHCl3-hexane and shaken at room temp. Lovastatin formation occurred at a rate of 3.2 .times. 10-5 mol/h-g lipase.

IT **159345-93-4**, Pravastatin diol lactone
RL: BPR (Biological process); RCT (Reactant); BIOL (Biological study); **PROC (Process)**
(synthesis of hydroxymethylglutaryl-CoA reductase inhibitors with lipase)

RN 159345-93-4 CAPLUS

CN 2H-Pyran-2-one, 6-[2-(1,2,6,7,8,8a-hexahydro-6,8-dihydroxy-2-methyl-1-naphthalenyl)ethyl]tetrahydro-4-hydroxy-, [1S-[1.alpha.(2S*,4S*),2.alpha.,6.alpha.,8.beta.,8a.alpha.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L8 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:68838 CAPLUS
DOCUMENT NUMBER: 120:68838
TITLE: Hepatoselective carrier-mediated sodium-independent uptake of pravastatin and pravastatin-lactone
AUTHOR(S): Ziegler, Kornelia; Hummelsiep, Silke
CORPORATE SOURCE: Institut fuer Pharmakologie und Toxikologie der Justus-Liebig Universitaet, Frankfurterstr. 107, Giessen, 35392, Germany
SOURCE: Biochim. Biophys. Acta (1993), 1153(1), 23-33
CODEN: BBACAQ; ISSN: 0006-3002
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Pravastatin and pravastatin-lactone are not taken up into extrahepatic cells such as fibroblasts, or hepatoma cells such as AS-30D ascites hepatoma cells or FAO cells. In contrast, pravastatin is taken up into isolated rat hepatocytes by a carrier mediated, saturable, temp.-dependent and energy-dependent mechanism. The kinetic parameters for the saturable uptake are Km 27 .mu.M, Vmax 537 pmol/mg per min. The permeability coeffs. were detd. to be 9.829.cntdot.10-7 cm/s at 4.degree.C, 1.76.cntdot.10-6 cm/s at 7.degree.C, 3.85.cntdot.10-6 cm/s at 17.degree.C and 5.82.cntdot.10-6 cm/s at 37.degree.C. The activation energy is 60 kJ/mol for 100 .mu.M pravastatin at 37.degree.C. The Q10 values are between 1.7 and 2.8. In the presence of metabolic inhibitors and in the absence of oxygen, transport is inhibited. Uptake of pravastatin is not dependent on an extracellular to intracellular sodium-gradient. Replacement of chloride by sulfate, nitrate, gluconate or thiocyanate significantly inhibits the uptake of pravastatin. Uptake is competitively inhibited by cholate and taurocholate in the presence and absence of sodium. Pravastatin, however, competitively inhibits the uptake of cholate and taurocholate only in the absence of sodium. In addn., pravastatin-lactone enters liver cells via an energy-dependent, carrier-mediated uptake system. For the saturable energy-dependent part of the hepatocellular uptake a Km value of 9 .mu.M and a Vmax value of 621 pmol/mg per min was detd. The permeability coeff. of pravastatin-lactone uptake is calcd. to be 5.41.cntdot.10-6 cm/s at 37.degree.C. The uptake of pravastatin-lactone is competitively-noncompetitively inhibited by pravastatin and by lovastatin and vice versa. These results indicate that the hepatoselectivity of pravastatin is due to its carrier-mediated uptake into rat hepatocytes via a sodium-independent bile acid carrier. Pravastatin-lactone resembles pravastatin-sodium in its hepatoselectivity.

IT **143289-89-8**, Pravastatin lactone

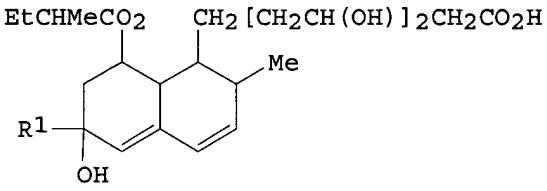
Golam Shameem

RL: **PROC (Process)**
(carrier-mediated uptake of, by hepatocytes)
RN 143289-89-8 CAPLUS

L8 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1983:516076 CAPLUS
DOCUMENT NUMBER: 99:116076
TITLE: Synergistic antichloesteremic activity of ML-236B derivatives
PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 16 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 58090509	A2	19830530	JP 1981-188530	19811125
JP 01005571	B4	19890131		

GI



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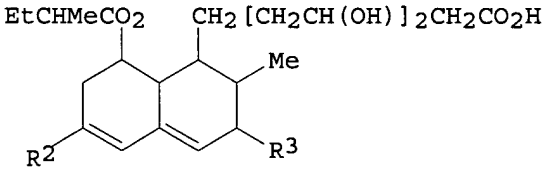
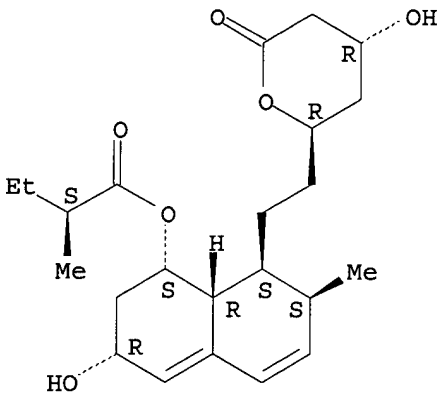


II

AB The carboxylic acids I or II (R1 and R2 = H or Me; R3 = H or OMe) (its salts, esters, and lactones) in combination with basic anion-exchange resins, which bind to bile acids, are synergistic anticholestermics. Thus, 20 mg III Na salt [87098-76-8]/kg/day or 1 g cholestyramine [11041-12-6] given orally to dogs decreased blood cholesterol 35 and 33%, resp., but the combined administration decreased it 76% in 4 wk.

IT **85956-23-6**
RL: **PROC (Process)**
(isolation of, as anticholestermic from Syncephalastrum nigricans)
RN 85956-23-6 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3-hydroxy-7-methyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	318.85	587.36

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-44.69	-44.69

STN INTERNATIONAL LOGOFF AT 18:21:20 ON 27 NOV 2001

DIALOG(R)File 399:CA SEARCH(R)

136058840 CA: 136(4)58840s PATENT
Method of stabilizing medicinal compositions containing pravastatin
INVENTOR(AUTHOR): Usui, Fusao; Yada, Shuichi; Kurihara, Kozo; Fukazawa, Toshio
LOCATION: Japan,
ASSIGNEE: Sankyo Company, Limited
PATENT: PCT International ; WO 200197800 A1 DATE: 20011227
APPLICATION: WO 2001JP5212 (20010619) *JP 2000188983 (20000623)
PAGES: 22 pp. CODEN: PIXXD2 LANGUAGE: Japanese CLASS: A61K-031/22A; A61K-047/02B; A61P-043/00B; A61P-003/06B DESIGNATED COUNTRIES: AU; BR; CA; CN; CO; CZ; HU; ID; IL; IN; KR; MX; NO; NZ; PL; RU; SG; SK; US; ZA
DESIGNATED REGIONAL: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; TR
SECTION:
CA263006 Pharmaceuticals
IDENTIFIERS: tablet pravastatin stabilizer magnesium aluminum silicate
DESCRIPTORS:
Drug delivery systems...
tablets; Mg or Al acid compds. for stabilizing pravastatin
CAS REGISTRY NUMBERS:
1327-43-1 12511-31-8 81093-37-0 81131-70-6 Mg or Al acid compds. for stabilizing pravastatin

2/5/2 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

136025124 CA: 136(2)25124h PATENT
Pravastatin sodium pharmaceuticals containing compounds capable of binding carbon dioxide
INVENTOR(AUTHOR): Pflaum, Zlatko; Milivojevic, Dusan; Rucman, Boris; Kogej, Stojan
LOCATION: Slovenia,
ASSIGNEE: Lek Pharmaceutical and Chemical Company D.D.
PATENT: PCT International ; WO 200193859 A1 DATE: 20011213
APPLICATION: WO 2000IB771 (20000609)
PAGES: 33 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-031/22A; A61K-031/366B; A61K-031/404B; A61K-047/02B DESIGNATED COUNTRIES: AE; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CR; CU; CZ; DE; DK; DM; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; TZ; UA; UG; US; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS ; MW; MZ; SD; SL; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG
SECTION:
CA263006 Pharmaceuticals
IDENTIFIERS: pravastatin pharmaceutical stabilization carbon dioxide
DESCRIPTORS:
Buffers... Drug delivery systems... Fuller's earth... Silica gel,biological studies... Stabilizing agents... Zeolites(synthetic),biological studies...
pravastatin sodium pharmaceuticals contg. compds. capable of binding carbon dioxide
CAS REGISTRY NUMBERS:
497-19-8 1310-58-3 1310-73-2 21645-51-2 biological studies, pravastatin sodium pharmaceuticals contg. compds. capable of binding carbon dioxide
9028-35-7 inhibitors; pravastatin sodium pharmaceuticals contg. compds.

capable of binding carbon dioxide
1310-65-2 7558-79-4 12030-88-5 81093-37-0 81131-70-6 93957-54-1
134523-00-5 145599-86-6 pravastatin sodium pharmaceuticals contg. compds. capable of binding carbon dioxide
124-38-9 processes, pravastatin sodium pharmaceuticals contg. compds. capable of binding carbon dioxide

2/5/3 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

135185491 CA: 135(13)185491h PATENT
Manufacture of pravastatin sodium tablets
INVENTOR(AUTHOR): Taniguchi, Toshiya; Terai, Takao; Ishizuka, Yasuhiro
LOCATION: Japan,
ASSIGNEE: Ohara Yakuhin Kogyo K. K.
PATENT: Japan Kokai Tokkyo Koho ; JP 2001233766 A2 DATE: 20010828
APPLICATION: JP 2000347383 (20000221) *JP 200042927 (20000221)
PAGES: 4 pp., Division of Jpn. Kokai Tokkyo Koho Appl. No. 00 42,927
CODEN: JKXXAF LANGUAGE: Japanese CLASS: A61K-031/22A; A61K-009/20B; A61K-047/02B; A61K-047/12B; A61K-047/26B; A61K-047/36B; A61K-047/38B; A61P-003/06B
SECTION:
CA263006 Pharmaceuticals
IDENTIFIERS: tablet pravastatin calcium silicate stabilizer
DESCRIPTORS:
Drug delivery systems...
tablets; stable tablets contg. pravastatin sodium
CAS REGISTRY NUMBERS:
9004-34-6 biological studies, cryst.; stable tablets contg. pravastatin sodium
9005-25-8 biological studies, stable tablets contg. pravastatin sodium
81131-70-6 1344-95-2 9050-04-8 557-04-0 stable tablets contg. pravastatin sodium

2/5/4 (Item 4 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

134114919 CA: 134(9)114919x PATENT
Microbial process for preparing pravastatin
INVENTOR(AUTHOR): Jekkel, Antonia; Ambrus, Gabor; Ilkoy, Eva; Horvath, Ildiko; Konya, Attila; Szabo, Istvan Mihaly; Nagy, Zsuzsanna; Horvath, Gyula; Mozes, Julia; Barta, Istvan; Somogyi, Gyorgy; Salat, Janos; Boros, Sandor
LOCATION: Hung.
ASSIGNEE: Gyogyszerkutato Intezet Kft.
PATENT: PCT International ; WO 0104340 A1 DATE: 20010118
APPLICATION: WO 2000HU66 (20000629) *HU 999902352 (19990712)
PAGES: 29 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12P-017/06A; C12P-007/42B DESIGNATED COUNTRIES: AE; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CR; CU; CZ; DE; DK; DM; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG
SECTION:
CA216002 Fermentation and Bioindustrial Chemistry
IDENTIFIERS: Micromonospora bioconversion pravastatin extn purifn

DESCRIPTORS:
Liquid chromatography...
adsorption; microbial process for prepg. pravastatin
Fermentation...
aerobic; microbial process for prepg. pravastatin
Hydroxylation...
biol.; microbial process for prepg. pravastatin
Fermentation...
broth; microbial process for prepg. pravastatin
Taxonomy...
chemotaxonomy, of Micromonospora isolates; microbial process for prepg. pravastatin
Extraction... Ion exchange chromatography... Lactonization...
Micromonospora echinospora echinospora... Micromonospora megalomicea nigra ... Micromonospora purpurea... Micromonospora rosaria... Micromonospora...
Silica gel,processes...
microbial process for prepg. pravastatin
Liquid chromatography...
supports, Dowex AL400; microbial process for prepg. pravastatin
CAS REGISTRY NUMBERS:
103-49-1 71359-07-4 71427-33-3 81093-37-0P 81131-70-6P 85956-22-5P 151061-40-4P microbial process for prepg. pravastatin
64-17-5 110-54-3 141-78-6 processes, microbial process for prepg. pravastatin
76-05-1 1310-73-2 reactions, microbial process for prepg. pravastatin

2/5/5 (Item 5 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

133182996 CA: 133(13)182996z PATENT
Stable pravastatin sodium tablets
INVENTOR(AUTHOR): Tatebe, Satoshi
LOCATION: Japan,
PATENT: Japan Kokai Tokkyo Koho ; JP 2000229855 A2 DATE: 20000822
APPLICATION: JP 99117389 (19990426) *JP 98366083 (19981207)
PAGES: 4 pp. CODEN: JKXXAF LANGUAGE: Japanese CLASS: A61K-031/235A; A61K-009/20B; A61P-003/06B; A61K-047/02B; A61K-047/24B; A61K-047/26B
SECTION:
CA263006 Pharmaceuticals
IDENTIFIERS: dry method tablet pravastatin mannitol, calcium hydrogenphosphate pravastatin tablet, magnesium aluminate metasilicate pravastatin tablet
DESCRIPTORS:
Hypolipemic agents...
stable pravastatin sodium tablets
Drug delivery systems...
tablets; stable pravastatin sodium tablets
CAS REGISTRY NUMBERS:
63-42-3 69-65-8 7757-93-9 12511-31-8 excipient; in stable pravastatin sodium tablets
81131-70-6 stable pravastatin sodium tablets

2/5/6 (Item 6 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

117258210 CA: 117(26)258210f PATENT
Purification of lovastatin and related compounds for pharmaceutical use
INVENTOR(AUTHOR): Haytko, Peter N.; Wildman, Arthur S., Jr.
LOCATION: USA

ASSIGNEE: Merck and Co., Inc.
PATENT: PCT International ; WO 9216276 A1 DATE: 921001
APPLICATION: WO 92US1864 (920309) *US 668831 (910313)
PAGES: 19 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: B01D-015/08A
DESIGNATED COUNTRIES: CA; JP; US DESIGNATED REGIONAL: AT; BE; CH; DE; DK ; ES; FR; GB; GR; IT; LU; MC; NL; SE
SECTION:
CA263005 Pharmaceuticals
CA207XXX Enzymes
IDENTIFIERS: lovastatin purifn HPLC pharmaceutical
DESCRIPTORS:
Chromatography,column and liquid, high-performance... Chromatography,column and liquid, high-performance reversed-phase...
for purifn. of lovastatin and related compds. for pharmaceutical uses
Anticholesteremics and Hypolipemics...
lovastatin and related compds. for, purifn. by HPLC of
CAS REGISTRY NUMBERS:
637-07-0 23288-49-5 25812-30-0 anticholesteremics contg. HPLC-purified HMG CoA reductase inhibitors and
59-67-6 biological studies, anticholesteremics contg. HPLC-purified HMG CoA reductase inhibitors and
57-88-5 biological studies, serum, lowering of, HMG CoA reductase inhibitors for, HPLC purifn. of
18623-11-5D conjugates with silica or carbon or polymers, as stationary phase in HPLC purifn. of lovastatin and related compds.
9029-62-3 9077-14-9 inhibitors of, anticholesteremics contg. HPLC-purified HMG CoA reductase inhibitors and
37250-24-1 inhibitors of, purifn. for pharmaceutical use of, by HPLC
73573-88-3 75330-75-5 79902-63-9 81093-37-0 93957-54-1 purifn. for pharmaceutical use of, by HPLC
9003-70-7 silane-coated, as chromatog. medium in HPLC purifn. of lovastatin and related compds. for pharmaceutical use
64-17-5 67-56-1 67-63-0 67-64-1 67-66-3 75-05-8 75-09-2 109-99-9 141-78-6 uses, in eluent for HPLC purifn. lovastatin and related compds. for pharmaceutical uses
7440-44-0 uses, porous, as chromatog. medium in HPLC purifn. of lovastatin and related compds. for pharmaceutical use
7631-86-9 uses, silane-coated, as chromatog. medium in HPLC purifn. of lovastatin and related compds. for pharmaceutical use

2/5/7 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

10360515 Genuine Article#: 518XJ Number of References: 14
Title: Effects of simvastatin on the phospholipid composition of high-density lipoproteins in patients with hypercholesterolemia
Author(s): Ozerova IN; Paramonova IV; Olfer'ev AM; Akhmedzhanov NM; Aleksandrova MA; Perova NV
Corporate Source: Russian Minist Hlth,State Res Ctr Prevent Med, Dept Metab Disorders,Moscow//Russia/
Journal: BULLETIN OF EXPERIMENTAL BIOLOGY AND MEDICINE, 2001, V132, N2 (AUG), P763-765
ISSN: 0007-4888 Publication date: 20010800
Publisher: CONSULTANTS BUREAU, 233 SPRING ST, NEW YORK, NY 10013 USA
Language: English Document Type: ARTICLE
Geographic Location: Russia
Journal Subject Category: MEDICINE, RESEARCH & EXPERIMENTAL
Abstract: We studied the phospholipid composition of high-density lipoproteins in patients with hypercholesterolemia before and after treatment with **simvastatin**. Individual phospholipids were separated by thin-layer chromatography on glass plates coated with

silica gel. It was found that apart from hypolipidemic effect, simivastatin changed the concentration and phospholipid composition of high-density lipoproteins, which improved their cholesterol-accepting and cholesterol-transporting properties.

Descriptors--Author Keywords: lipoproteins ; phospholipids ; hypercholesterolemia ; simvastatin

Identifiers--KeyWord Plus(R): CHOLESTEROL; EFFLUX; HDL

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ASSMANN G, 1983, V29, P2026, CLIN CHEM
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COLLES SM, 2000, V41, P1185, J LIPID RES
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FOURNIER N, 1996, V37, P1704, J LIPID RES
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SLOTTE JP, 1990, V1025, P152, BIOCHIM BIOPHYS ACTA
SVANBORG A, 1961, V169, P43, ACTA MED SCAND
VASKOVSKY VE, 1975, V114, P129, J CHROMATOGR

?

2/5/8 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

10018801 Genuine Article#: 476BC Number of References: 5
Title: Validated analysis of fluvastatin in a pharmaceutical capsule formulation and serum by capillary electrophoresis
Author(s): Dogrukol-Ak D; Kircali K; Tuncel M; Aboul-Enein HY (REPRINT)
Corporate Source: King Faisal Specialist Hosp & Res Ctr,Dept Biol & Med Res , Pharmaceut Anal Lab, MBC 03,POB 3354/Riyadh 11211//Saudi Arabia/ (REPRINT); King Faisal Specialist Hosp & Res Ctr,Dept Biol & Med Res, Pharmaceut Anal Lab, MBC 03,Riyadh 11211//Saudi Arabia/; Univ Anadolu,Fac Pharm, Dept Analyt Chem,TR-26470 Tepebasi/Eskisehir/Turkey/
Journal: BIOMEDICAL CHROMATOGRAPHY, 2001, V15, N6 (OCT), P389-392
ISSN: 0269-3879 Publication date: 20011000
Publisher: JOHN WILEY & SONS LTD, BAFFINS LANE CHICHESTER, W SUSSEX PO19 1UD, ENGLAND
Language: English Document Type: ARTICLE
Geographic Location: Saudi Arabia; Turkey
Journal Subject Category: BIOCHEMICAL RESEARCH METHODS; BIOCHEMISTRY & MOLECULAR BIOLOGY; CHEMISTRY, ANALYTICAL; PHARMACOLOGY & PHARMACY
Abstract: The capillary electrophoretic behavior and the determination of **fluvastatin** (FLU) in capsule and serum is described in this study. Method development was conducted in a fused-**silica** capillary (L = 86 cm, L-eff = 58 cm and 75 mum i.d.) and a background electrolyte consisting of 10 mM borate at pH 8 was used. The separation was per-formed by current-controlled system applying 41 muA, detecting at 239 nm and injecting 0.5 s vacuum injection. A good electropherogram and excellent repeatability was obtained. FLU and phenobarbital sodium (internal standard) migrated (with RSD%) at 4.8 (0.3) min and 5.2 (0.6.) min, respectively. Limit of detection (LOD) and Iii-nit of quantitation (LOQ) values were found to be 1 x 10(-6) M and 2.89 x 10(-6) M, respectively. Linearity in the range of 1.03 x 10(-5) -5.15 x 10(-5) M was examined employing intra-day and inter-day studies and well-correlated calibration equations were obtained. FLU in a capsule (Lescol(R) 40 mg declared) was found to be 41.9 +/-0.4 mg. Furthermore, FLU was determined in serum applying standard addition technique. Good repeatability and no interference were observed. The method proposed is simple, sensitive, precise and easy to use for the determination of FLU in capsule and serum. Copyright (C) 2001 John Wiley & Sons, Ltd.
Identifiers--KeyWord Plus(R): BLOOD-PLASMA; ENANTIOMERS
Cited References:
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TORESON H, 1997, V45, P29, CHROMATOGRAPHIA S
TORESON H, 1996, V729, P13, J CHROMATOGR A

2/5/9 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07669761 Genuine Article#: 194PK Number of References: 6
Title: Feasibility of lovastatin analysis by packed column supercritical fluid chromatography with ultraviolet detection
Author(s): Strode JTB; Taylor LT (REPRINT) ; Howard AL; Ip D
Corporate Source: VIRGINIA POLYTECH INST & STATE UNIV,COLL ARTS & SCI, DEPT CHEM, 107 DAVIDSON HALL/BLACKSBURG//VA/24061 (REPRINT); VIRGINIA POLYTECH INST & STATE UNIV,COLL ARTS & SCI, DEPT CHEM/BLACKSBURG//VA/24061; MERCK RES LABS,/W POINT//PA/19486
Journal: JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS, 1999, V20, N1-2

(JUN), P137-143
ISSN: 0731-7085 Publication date: 19990600
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND
Language: English Document Type: ARTICLE
Geographic Location: USA
Subfile: CC LIFE--Current Contents, Life Sciences
Journal Subject Category: PHARMACOLOGY & PHARMACY; CHEMISTRY, ANALYTICAL
Abstract: A reliable supercritical fluid chromatography (SFC) method was developed for the analysis of lovastatin, a hypocholesterolaemic drug, from MEVACOR(R). Methanol-modified carbon dioxide was shown to elute the drug, and its dehydrolovastatin and hydroxy acid **lovastatin** degradation products from a Hypersil(R) **silica** column. However, the hydroxy acid **lovastatin** was found to tail in this mobile phase. The phenomena was eliminated by the addition of trifluoroacetic acid [Haouck, S. Thomas, D. K. Ellison, Talanta 40 (1993) 491] to the mobile phase which permitted the drug and its two main degradation products to all elute from the Hypersil(R) silica column in under 6 min with symmetrical peak shape. Chromatographic limit of detection (LOD) and limit of quantification (LOQ), linear dynamic range (LDR), and injection precision were obtained in order to assess the chromatographic performance of the SFC system for the lovastatin separation.
Descriptors--Author Keywords: lovastatin analysis ; supercritical fluid chromatography ; ultraviolet detection
Identifiers--KeyWord Plus(R): MEVINOLINIC ACID
Cited References:
GULLO VP, 1981, V212, P239, J CHROMATOGR
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2/5/10 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02813805 Genuine Article#: MF520 Number of References: 4
Title: THE ISOLATION OF LOVASTATIN AND ITS DETERMINATION BY DENSITOMETRIC TLC AND BY HPLC
Author(s): KONFINO M; DELTCHEVA S; MINDJOVA K
Corporate Source: CHEM PHARMACEUT RES INST,3 KL OHRIDSKI/BU-1156 SOFIA//BULGARIA/
Journal: JPC-JOURNAL OF PLANAR CHROMATOGRAPHY-MODERN TLC, 1993, V6, N5 (SEP-OCT), P404-406
ISSN: 0933-4173
Language: ENGLISH Document Type: ARTICLE
Geographic Location: BULGARIA
Subfile: SciSearch; CC PHYS--Current Contents, Physical, Chemical & Earth Sciences
Journal Subject Category: CHEMISTRY, ANALYTICAL
Abstract: Lovastatin is a fungal metabolite which has been found to be an active competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase); as such it is a useful hypocholesterolemic and hypolemic agent.

The compound has been isolated from fermentation broths of Aspergillus terreus: methods employing HPLC and densitometric TLC have been developed for controlling all steps of the isolation of lovastatin, both as the lactone and as the free hydroxy acid. The end product was closely examined and characterized.

Descriptors--Author Keywords: **SILICA** GEL TLC ; QUANTITATIVE DENSITOMETRY ; HPLC ; **LOVASTATIN**
Identifiers--KeyWords Plus: REDUCTASE
Research Fronts: 91-0484 001 (PRIMARY HYPERCHOLESTEROLEMIA; REGRESSION OF CORONARY ATHEROSCLEROSIS; LONG-TERM CLINICAL TOLERANCE; HMG-COA REDUCTASE INHIBITION; SECONDARY PREVENTION)
Cited References:
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2/5/11 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

00997184 Genuine Article#: FM030 Number of References: 31
Title: QUANTITATIVE STUDIES OF TRANSFER INVIVO OF LOW-DENSITY, SF-12-60, AND SF-60-400 LIPOPROTEINS BETWEEN PLASMA AND ARTERIAL INTIMA IN HUMANS
Author(s): SHAIKH M; WOOTTON R; NORDESTGAARD BG; BASKERVILLE P; LUMLEY JS; LAVILLE AE; QUINEY J; LEWIS B
Corporate Source: RIGSHOSP,DEPT CLIN CHEM,KK 3011,BLEGDAMSVEJ 9/DK-2100 COPENHAGEN//DENMARK/; UNITED MED & DENT SCH GUYS & ST THOMAS HOSP,DEPT CHEM PATHOL & METAB DISORDERS/LONDON//ENGLAND/; HAMMERSMITH HOSP,DEPT MED PHYS/LONDON W12 0HS//ENGLAND/; ST BARTHOLOMEWS HOSP,DEPT SURG/LONDON EC1A 7BE//ENGLAND/; ST THOMAS HOSP,RAYNE INST/LONDON SE1 7EH//ENGLAND/
Journal: ARTERIOSCLEROSIS AND THROMBOSIS, 1991, V11, N3, P569-577
Language: ENGLISH Document Type: ARTICLE
Geographic Location: DENMARK; ENGLAND
Subfile: SciSearch; CC LIFE--Current Contents, Life Sciences
Journal Subject Category: CARDIOVASCULAR SYSTEM
Abstract: To assess the potential of various plasma lipoprotein classes to contribute to the lipid content of the arterial intima, influx and efflux of these plasma lipoprotein fractions into and from the intima of human carotid arteries were measured in vivo. While low density lipoprotein (LDL) is known to transfer from plasma into the arterial wall, there is less information on the atherogenic potential of lipoproteins of intermediate density (Sf 12-60) or of very low density (Sf 60-400). Aliquots of the same lipoprotein (LDL, Sf 12-60 lipoprotein particles, or Sf 60-400 lipoprotein particles) iodinated with iodine-125 and iodine-131 were injected intravenously 18-29 hours and 3-6 hours, respectively, before elective surgical removal of atheromatous arterial tissue, and the intimal clearance of lipoproteins, lipoprotein influx, and fractional loss of newly entered lipoproteins were calculated. Intimal clearance of Sf 60-400 particles was not detectable (< 0.3-mu-l x hr-1 x cm-2), whereas the average value for both LDL and Sf 12-60 lipoprotein particles was 0.9-mu-l x hr-1 x cm-2. Since the fractional loss of newly entered LDL and Sf 12-60 lipoprotein particles was also similar, the results suggest similar modes of entry and exit for these two particles. However, due to lower plasma concentrations of Sf 12-60 lipoproteins as compared with LDL, the mass influx of cholesterol in the Sf 12-60 particles was on the order of one 10th of that in LDL, and that of apolipoprotein B was about one 20th. The present results suggest that elevated plasma concentrations of Sf 12-60 or "remnant" lipoproteins share with LDL the potential for causing lipid accumulation in the arterial intima in humans.
Descriptors--Author Keywords: LOW DENSITY LIPOPROTEINS; INTERMEDIATE DENSITY LIPOPROTEINS; VERY LOW DENSITY LIPOPROTEINS; ARTERIAL WALL LIPOPROTEIN INTERACTION; ARTERIAL INFLUX EFFLUX OF LIPOPROTEINS
Identifiers--KeyWords Plus: CHOLESTEROL-FED RABBITS; CORONARY

HEART-DISEASE; HUMAN AORTIC TISSUE; FLUX; HYPERLIPOPROTEINEMIA; ATHEROSCLEROSIS; METABOLISM; INFLUX; SIZE
Research Fronts: 89-2539 002 (LOW-DENSITY LIPOPROTEIN METABOLISM; LDL RECEPTOR; RAT AORTIC SMOOTH-MUSCLE CELLS)
89-0474 001 (HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA; CORONARY HEART-DISEASE PREVENTION; CHOLESTEROL MANAGEMENT; SIMVASTATIN (MK 733); LIPID-LOWERING DRUGS)
89-3753 001 (HIGH-DENSITY LIPOPROTEIN CHOLESTEROL; RISK FACTOR FOR CORONARY HEART-DISEASE; HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA)
89-5871 001 (LOW-DENSITY LIPOPROTEIN RECEPTOR IN FAMILIAL HYPERCHOLESTEROLEMIA; APOLIPOPROTEIN-B GENE LOCUS INFLUENCES SERUM LDL CHOLESTEROL LEVEL; **SIMVASTATIN** (MK 733))
89-7553 001 (SIMPLEX OPTIMIZATION; KNOWLEDGE-BASED DESIGN AID FOR SUPERHEATERS EMPLOYING PSEUDO-RANDOM SEARCH; AUTOMATED DUAL **SILICA** TUBE ATOM TRAPPING)
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STONE NJ, 1974, V49, P476, CIRCULATION
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2/5/12 (Item 1 from file: 305)
DIALOG(R)File 305:Analytical Abstracts

340881 AA Accession No.: 64-24-G-10156 DOC. TYPE: Journal
Validated analysis of fluvastatin in a pharmaceutical formulation and serum by capillary electrophoresis.
AUTHOR: Dogrukol-Ak, D. ; Kircali, K. ; Tuncel, M. ; Aboul-Enein, H. Y.*

CORPORATE SOURCE: enein@kfshrc.edu.sa, Pharm. Anal. Lab., Biol. and Med. Res. Dept., King Faisal Specialist Hospital and Res. Centre, Riyadh 11211, Saudi Arabia
JOURNAL: Biomed. Chromatogr., (Biomedical Chromatography), Volume: 15, Issue: 6, Page(s): 389-392

CODEN: BICHE2 ISSN: 0269-3879
PUBLICATION DATE: Oct 2001 (20011000) LANGUAGE: English
ABSTRACT: The capillary electrophoretic behaviour and the determination of **fluvastatin** (FLU) in capsule and serum is described in this study. Method developed was conducted in a fused-**silica** capillary (86 cm x 75 .mu.m i.d., effective length 58 cm) and a background electrolyte of 10mM-borate of pH 8 was used. The separation was performed by the current-controlled system applying 41 .mu.A. detecting at 239 nm and injecting for 0.5 s by vacuum injection. A good electropherogram and excellent reproducibility were obtained. FLU and phenobarbital sodium (internal standard) migrated (with RSD%) at 4.8 (0.3) and 5.2 (0.6) min, respectively. Limit of detection and limit of quantification values were found to be 1 and 2.89 .mu.M, respectively. Linearity in the range of 10.3-51.5 .mu.M was examined employing intra-day and inter-day studies and well correlated calibration equations were obtained. FLU in a capsule (Lescol, 40 mg declared) was found to be 41.9 +/- 0.4 mg. Furthermore, FLU was determined in serum applying standard addition technique. Good repeatability and no interference were observed. The method proposed is simple, sensitive, precise and easy to use for the determination of FLU in capsule and serum.
IDENTIFIERS: electrophoresis, capillary zone (CZE)
ANALYTE: fluvastatin (93957-54-1) --detmn. of, in pharmaceuticals and serum, by CZE
MATRIX: blood serum
pharmaceutical preparations --detmn. of fluvastatin in, by CZE
SECTION: G-11801 (Pharmaceutical Analysis)

2/5/13 (Item 2 from file: 305)
DIALOG(R)File 305:Analytical Abstracts

319027 AA Accession No.: 63-02-G-10163 DOC. TYPE: Journal
Determination of lovastatin in human plasma by GC-MS.
AUTHOR: Zheng, W. H. ; Cai, K. H. ; Wu, Y. L.
CORPORATE SOURCE: Mol. Med. Res. Centre, Sun Yat-sen Univ. Sci., Guangzhou 510089, China
JOURNAL: Fenxi Ceshi Xuebao, (Fenxi Ceshi Xuebao), Volume: 19, Issue: 4, Page(s): 69-70
CODEN: FCEXES ISSN: 1004-4957
PUBLICATION DATE: Jul 2000 (20000700) LANGUAGE: Chinese
ABSTRACT: Plasma (1 ml) was vortexed with 100 .mu.l simvastatin (0.28 mg/l; internal standard) in acetonitrile for 1 min and the mixture was left to stand for 30 min. The mixture was extracted with 3 ml ethyl acetate for 1 min and centrifuged for 20 min. A 2 ml portion of the supernatant solution was evaporated to dryness and the residue was dissolved in 50 .mu.l acetonitrile. Portions (2 .mu.l) of the solution were analysed for **lovastatin** (I) by GC on a high-performance fused-**silica** column (12 m x 0.2 mm i.d.) coated with HP-1 (0.33 .mu.m), operated with temperature programming from 60.degree.C (held for 2 min) to 300.degree.C at 20.degree.C/min and 70 eV EIMS detection operated selected-ion monitoring mode. The calibration graph for I was linear from 0.36-48 mg/l, with detection limit of 0.1 mg/l. The recoveries were 92-101%. Intra-and inter-day RSD were 3.1-5 and 5.5-8.9%, respectively.
IDENTIFIERS: chromatography, gas (GC) ; mass spectrometry (MS)
ANALYTE: lovastatin (75330-75-5) --detmn. of, in plasma, by GC-MS
MATRIX: blood plasma --detmn. of lovastatin in, by GC-MS
SECTION: G-20002 (Pharmaceutical Analysis)

2/5/14 (Item 3 from file: 305)
DIALOG(R)File 305:Analytical Abstracts

305143 AA Accession No.: 62-08-G-10249 DOC. TYPE: Journal
Analysis method and pharmacokinetic studies of simvastatin in plasma.
AUTHOR: Cai, K. H. ; Zheng, W. H. ; Zhou, Y. ; Lin, G. Y. ; Zhao, X. L.

CORPORATE SOURCE: Mol. Med. Res. Centre, Dept. Clinical Pharmacol., Sun Yat Sen Univ. Sci., Guangzhou 510089, China
JOURNAL: Fenxi Huaxue, (Fenxi Huaxue), Volume: 27, Issue: 11, Page(s): 1254-1257
CODEN: FHHHDT ISSN: 0253-3820
PUBLICATION DATE: 20 Nov 1999 (19991120) LANGUAGE: Chinese
ABSTRACT: Plasma (1 ml) was vortexed with 15 ng lovastatin (internal standard) for 1 min then with 3 ml ethyl acetate for 1 min; after storing for 30 min and centrifugation for 20 min, 2 ml the supernatant solution was evaporated and the residue was dissolved in 50 .mu.l acetonitrile. Portions (2 .mu.l) of the solution were analysed for **simvastatin** (I) by GC on a fused-**silica** column (12 m x 0.2 mm i.d.) coated with HP-1 (0.33 .mu.m), operated with temperature programming from 60.degree.C (held for 2 min) to 210.degree.C (for 0.5 min) at 35.degree.C/min and then to 280.degree.C (held for 10 min) at 4.degree.C/min, carrier gas (not stated) and 70 eV EIMS detection operated in selected-ion monitoring mode at m/z 159 and 199 for I. The calibration graph for I was linear from 0.27-54 .mu.g/l. Recoveries of 0.9-27 .mu.g/l of added I to drug-free plasma samples were in the range 96-103%. Intra-and inter-day RSD (n = 5) were <5.2%. The method was used in the pharmacokinetic studies of I.
IDENTIFIERS: chromatography, gas (GC) ; mass spectrometry (MS)
ANALYTE: simvastatin (79902-63-9) --detmn. of, in plasma, by GC-MS
MATRIX: blood plasma --detmn. of simvastatin in, by GC-MS
SECTION: G-20002 (Pharmaceutical Analysis)
?